

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

OTSUKA PHARMACEUTICAL CO., LTD.,

Plaintiff,

v.

SANDOZ, INC.,
TEVA PHARMACEUTICALS USA, INC.,
TEVA PHARMACEUTICAL INDUSTRIES
LTD.,
BARR LABORATORIES, INC., BARR
PHARMACEUTICALS, INC.,
APOTEX CORP., APOTEX INC.,
SUN PHARMACEUTICAL INDUSTRIES, LTD.,
SYNTHON HOLDING BV, SYNTHON BV,
SYNTHON PHARMACEUTICALS, INC., and
SYNTHON LABORATORIES, INC.,

Defendants.

HON. MARY L. COOPER

Civil Action No. 07-cv-1000 MLC (LHG)

**FINAL PRETRIAL ORDER
(PROPOSED)**

This matter having come before the Court for a pretrial conference pursuant to Fed. R. Civ. P. 16; and John F. Brenner of Pepper Hamilton, LLP, and James B. Monroe, Michael J. Flibbert, Paul W. Browning, and Denise Main of Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, and Robert L. Baechtold and John D. Murnane of Fitzpatrick, Cella, Harper & Scinto, having appeared for plaintiff Otsuka Pharmaceutical Co., Ltd. ("Otsuka"); and Mayra V. Tarantino of Lite DePalma Greenberg, LLC, Elizabeth Holland, Maria Luisa Palmese, and Thomas F. Lavery, IV of Kenyon & Kenyon LLP, having appeared for defendants Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries, Ltd., Barr Laboratories, Inc., and Barr Pharmaceuticals, LLC, and Jeffrey A. Cohen of Flaster/Greenberg, P.C., James P. White, Hartwell P. Morse, III, and Steven E. Feldman of Husch, Blackwell, Sanders LLP, Welsh & Katz, having appeared for defendants Apotex, Inc. and Apotex Corp.; the following Final Pretrial Order is hereby entered:

1. JURISDICTION (set forth specifically).

1. This is a civil action for infringement of U.S. Patent No. 5,006,528 ("the '528 patent"), arising under the United States patent laws, Title 35, United States Code, § 100 *et seq.*, including 35 U.S.C. §§ 271 and 281. This Court has subject matter jurisdiction under 28 U.S.C. §§ 1331 and 1338(a).

2. For purposes of this civil action only, no party contests venue or personal jurisdiction.

2. PENDING/CONTEMPLATED MOTIONS (Set forth all pending or contemplated motions, whether dispositive or addressed to discovery or to the calendar. Also, set forth the nature of the motion and the return date. If the Court indicated that it would rule on any matter at pretrial, summarize that matter and each party's position).

The briefing schedule for contemplated motions *in limine* and/or *Daubert* motions shall be set at the Pretrial Conference. All contemplated motions *in limine* and/or *Daubert* motions are identified below.

A. PENDING MOTIONS

No motions are pending.

B. OTSUKA'S CONTEMPLATED MOTIONS¹

Otsuka intends to file the following motions *in limine* and/or *Daubert* motions, on the schedule set by the Court:

1. A motion to exclude all evidence by Defendants regarding publications and information that do not qualify as prior art to the '528 patent under 35 U.S.C. §§ 102/103.

¹ The parties have listed their contemplated motions separately and Otsuka does not concede that any of Defendants' contemplated motions are proper motions *in limine* and/or *Daubert* motions. Defendants also do not concede that any of Plaintiff's contemplated motions are proper motions *in limine* and/or *Daubert* motions.

2. A motion to exclude all testimony by Defendants' experts relating to: (1) schizophrenia, clinical studies in humans relating to antipsychotic drugs, the efficacy or side effects of antipsychotic drugs, the design, synthesis and/or testing of antipsychotic drugs; (2) the alleged materiality of any information allegedly withheld from or misrepresented to the United States Patent and Trademark Office ("PTO") and/or any alleged intent to deceive the PTO; and (3) issues of law.

C. DEFENDANTS' CONTEMPLATED MOTIONS

1. Defendants' Contemplated Motions To Be Brought Before Trial

ALL
IN Limine

1. A motion to exclude evidence regarding secondary considerations, including commercial success, long felt need, and copying, as not probative of non-obviousness under 35 U.S.C. § 103.

2. A motion to exclude exhibits and deposition designations originating from the stayed defendants Sandoz, Inc. and Sun Pharmaceuticals Industries, Ltd.

3. A motion or cross-motion to likewise limit or exclude testimony by Plaintiff's experts beyond the subject matters that Defendants' experts are permitted to testify about by the Court in the event that the Court limits or excludes any testimony by Defendants' experts in response to any motion in limine and/or Daubert motion filed by Plaintiff.

4. A motion to exclude or limit the testimony of Plaintiff's late disclosed witness, Mr. Mark Altmeyer.

2. Defendants' Contemplated Issues To Be Addressed In The Trial Brief

ALL IN
trial
brief

1. Apotex contemplates addressing the issue of whether the presumption of validity (35 U.S.C. § 282) requires that invalidity be proved by clear and convincing evidence or a

preponderance of the evidence, and whether the presumption of validity applies when invalidity is based on information not considered by the PTO.²

2. A motion to exclude the findings in the *Janssen* case to the extent Otsuka seeks to rely on them as evidence because they are irrelevant and inadmissible hearsay and the *Janssen* case has neither res judicata nor collateral estoppel effect in this action.

3. A motion that the obviousness analysis does not require the selection of a “lead compound.”

4. A motion to sequester all fact witnesses.

² Apotex recognizes that there is contrary case law from the Federal Circuit. Counsel for Apotex states, after a reasonable inquiry under the circumstances, that the issue to be briefed is warranted by a nonfrivolous argument for modifying or reversing existing law on this issue.

3. STIPULATION OF FACTS (Set forth in narrative form a comprehensive listing of all uncontested facts, including all answers to interrogatories and admissions, to which there is agreement among the parties).

The parties admit the following facts, which require no proof at trial.

THE PARTICIPATING PARTIES

1. Plaintiff Otsuka is a corporation organized and existing under the laws of Japan with its corporate headquarters at 2-9 Kanda Tsukasa-machi, Chiyoda-ku, Tokyo, 101-8535, Japan.

2. Defendant Teva Pharmaceuticals USA, Inc. ("Teva USA") is a Delaware corporation with a principal place of business in North Wales, Pennsylvania.

3. Defendant Barr Laboratories, Inc. ("Barr Labs.") is a Delaware corporation having a principal place of business in Woodcliff Lake, New Jersey. Barr Labs. is a wholly owned direct subsidiary of Barr Pharmaceuticals, LLC.

4. Defendant Barr Pharmaceuticals, Inc. was acquired by Teva USA on December 23, 2009, and changed its name to Barr Pharmaceuticals, LLC. Barr Pharmaceuticals, LLC is a Delaware limited liability company with a principal place of business in North Wales, Pennsylvania and is a wholly-owned subsidiary of Teva USA. Defendants Barr Labs. and Barr Pharmaceuticals, LLC are collectively referred to herein as "Barr."

5. Defendant Apotex Corp. is a Delaware corporation with a principal place of business in Weston, Florida. Defendant Apotex Inc. is a Canadian corporation with a principal place of business in Toronto, Canada. Defendants Apotex Corp. and Apotex Inc. are collectively referred to herein as "Apotex."

THE STAYED PARTIES

6. Defendant Sandoz, Inc. ("Sandoz") has stipulated to a stay of this consolidated action, Civil Action No. 07-cv-01000, according to the terms set forth in Docket Index ("D.I.") 310.

7. Defendant Sun Pharmaceutical Industries, Ltd. ("Sun") has stipulated to a stay of Civil Action No. 07-cv-01516, now consolidated under this action, according to the terms set forth in D.I. 285 in this consolidated action.

8. Defendants Synthon Holding BV, Synthon BV, Synthon Pharmaceuticals, Inc., and Synthon Laboratories, Inc. (collectively "Synthon") have stipulated to a stay of Civil Action No. 07-cv-04112, now consolidated under this action, according to the terms set forth in D.I. 92 in this consolidated action.

9. As set forth in the Orders entered at D.I. 310, D.I. 285 and D.I. 92, respectively, in this consolidated action, Defendants Sandoz, Sun and Synthon have agreed to be bound by the final judgment in this case regarding the validity and enforceability of the '528 patent.

10. Zydus Pharmaceuticals USA, Inc. and Cadila Healthcare Ltd. are parties to actions in this District, Civil Action Nos. 08-cv-02675(MLC) ("Zydus Action I") and 10-cv-02857 ("Zydus Action II"), not consolidated with the present action. In Zydus Action I, the parties have agreed to be bound by the final judgment in this case regarding the validity and enforceability of the '528 patent according to the stipulated order entered at D.I. 10 in Zydus Action I.

THE DISMISSED PARTIES

11. Defendant Teva Pharmaceutical Industries, Ltd. ("Teva Industries") is a corporation organized under the laws of Israel with its principal place of business located at 5

Basel Street, P.O. Box 3190, Petach Tikva 49131, Israel. Teva USA is a wholly owned indirect subsidiary of Teva Industries. Teva Industries has been dismissed as a party to this action but has stipulated to be bound by any judgment, order or decision in Civil Action No. 07-cv-1000 that one or more claims of the '528 patent are not invalid and/or not unenforceable, and/or are infringed by the generic aripiprazole products Teva USA seeks FDA approval for pursuant to ANDA Nos. 78-607, 78-608 and 78-708. *See* D.I. 15 in 07-cv-01110, now consolidated with this action, and D.I. 70 in this consolidated action.

PATENT IN SUIT

12. The '528 patent, entitled "Carbostyryl Derivatives," issued on April 9, 1991. Otsuka is the owner of the '528 patent.

13. Yasuo Oshiro, Seiji Sato, and Nobuyuki Kurahashi are the named inventors of the '528 patent.

14. Yasuo Oshiro graduated from the Toyama University's Department of Industrial Chemistry, Institute of Technology. He also received a doctorate in applied chemistry from Osaka University. He was employed as a researcher at Otsuka at the time the patent application leading to the '528 patent was filed.

15. Seiji Sato received a master's degree in synthetic organic chemistry from the Graduate School of Pharmaceutical Sciences, Tohoku University. He was employed as a researcher at Otsuka at the time the patent application leading to the '528 patent was filed.

16. Nobuyuki Kurahashi received a master's degree in Pharmaceutical Sciences from the Gifu Pharmaceutical University Graduate School where he specialized in synthetic organic chemistry. He was employed as a researcher at Otsuka at the time the patent application leading to the '528 patent was filed.

17. The '528 patent issued from U.S. Patent Application No. 424,719 ("the '719 application") filed on October 20, 1989, which claimed priority from Japanese Application No. 63-276953, filed on October 31, 1988.

18. The PTO issued a Reexamination Certificate for the '528 patent on June 13, 2006.

19. Otsuka has asserted claims 12, 17 and 23 of the '528 patent against Defendants in this action.

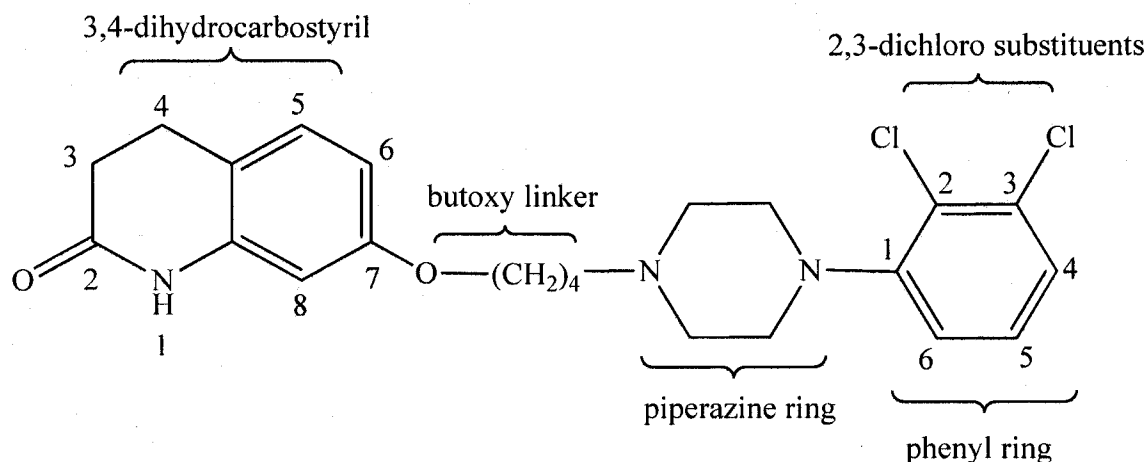
20. Claim 12 of the '528 patent is directed to the compound aripiprazole, which has the chemical name 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydrocarbostyryl.

21. Claim 17 of the '528 patent is directed to a pharmaceutical composition for treating schizophrenia containing, as the active ingredient, aripiprazole or a pharmaceutically acceptable salt thereof.

22. Claim 23 of the '528 patent is directed to a method of treating schizophrenia comprising administering a pharmaceutical composition containing, as an active ingredient, aripiprazole or a salt thereof.

ARIPIPAZOLE

23. The structure of aripiprazole is:



24. Aripiprazole is a carbostyryl derivative.

25. Aripiprazole is a 7-position carbostyryl derivative.
26. Aripiprazole has a butoxy linker.
27. Aripiprazole contains a phenyl ring with a 2-chloro substituent and a 3-chloro substituent.

OTSUKA'S NEW DRUG APPLICATIONS

28. Otsuka is the holder of New Drug Application ("NDA") No. 21-436 for aripiprazole tablets, which the Food and Drug Administration ("FDA") approved on November 15, 2002. Otsuka currently lists the '528 patent in Approved Drug Products with Therapeutic Equivalence Evaluations ("the Orange Book") for NDA No. 21-436. Otsuka had also listed U.S. Patent No. 4,734,416 ("the '416 patent") in the Orange Book for NDA No. 21-436.

29. Otsuka markets its aripiprazole formulations that are the subjects of NDA No. 21-436 under the trade name Abilify®.

DEFENDANTS' ABBREVIATED NEW DRUG APPLICATIONS

30. Defendants filed with each Abbreviated New Drug Application ("ANDA") identified below a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV), commonly referred to as a "Paragraph IV certification," with respect to the '528 patent.

31. Teva USA filed ANDA Nos. 78-607, 78-608, and 78-708 under Section 505(j) of the Federal Food, Drugs and Cosmetic Act, 21 U.S.C. § 355(j) ("the Act") seeking FDA approval to market generic tablet products containing 2 and 5 mg (No. 78-607); 10 mg (No. 78-608); and 15, 20 and 30 mg (No. 78-708) of aripiprazole.

32. Apotex Corp. filed ANDA No. 78-583 under Section 505(j) of the Act seeking FDA approval to market generic tablet products containing 5, 10, 15, 20 and 30 mg of aripiprazole. Apotex Corp. amended its ANDA No. 78-583 seeking FDA approval to market

generic tablet products containing 2 mg of aripiprazole in addition to Apotex Corp.'s 5, 10, 15, 20 and 30 mg generic tablet products.

33. Barr Labs. filed ANDA Nos. 78-612 and 78-613 under Section 505(j) of the Act seeking FDA approval to market generic tablet products containing 2, 5, 10, 15, 20 and 30 mg of aripiprazole.

34. The lawsuits against each of the Defendants were consolidated on June 27, 2007, with the exception of Otsuka's action (Civil Action No. 08-cv-04958-MLC) against Apotex's amended ANDA No. 78-583, which was consolidated with this action on December 11, 2008. *See* Civil Action No. 08-cv-04958(MLC) at D.I. 13.

STIPULATION OF INFRINGEMENT

35. Teva USA, Apotex, and Barr have stipulated as follows:

(1) Aripiprazole Tablets disclosed in [Defendants' respective ANDA Nos. as described in paragraphs 31-33], if commercially made, used, offered for sale or sold within the United States, or commercially imported into the United States, would fall within the scope of Claims 12, 17 and 23 of U.S. Patent No. 5,006,528 to the extent those claims are valid and enforceable.

(2) The purpose of the present Stipulation is to streamline expert discovery and trial. The Stipulation shall not be used by Otsuka for any purpose in this litigation other than to relieve Otsuka of the burden of proving infringement during expert discovery and at trial. This stipulation only applies to Otsuka's currently-pled infringement allegations under 35 U.S.C. 271(e)(2)(A) and does not apply to any allegation of direct or indirect infringement that Otsuka may bring in this matter or in another matter in the future. This stipulation will not be used in any way to support any allegation or willful and/or exceptional case by Otsuka in this matter or in any other matter in the future.

See D.I. 224, D.I. 226 and D.I. 233 in this consolidated action.

36. Defendants Sun and Sandoz, stayed parties to this consolidated action, have also agreed to the same stipulation. *See* D.I. 223 and D.I. 225 in this consolidated action.

4. PLAINTIFF'S CONTESTED FACTS: (Stated separately for each defendant. Proof shall be limited at trial to the matters set forth below. Failure to set forth any matter shall be deemed a waiver thereof.)³

(1) Plaintiff intends to prove the following facts with regard to liability:

1. Defendants have stipulated to infringement of the asserted patent claims and therefore Otsuka need not prove infringement at trial. Moreover, because the '528 patent is presumed valid, Otsuka has no burden of proof regarding Defendants' affirmative defenses and counterclaims that the asserted patent claims are invalid or unenforceable. Defendants must prove those affirmative defenses and counterclaims by clear and convincing evidence. Without assuming any burden of proof, Otsuka expects the Defendants to contest the facts below. Otsuka's statement of contested facts applies equally to each of the Defendants. Should the Court determine that any issue of fact identified below is more properly considered an issue of law, it should be so considered.

A. FACTUAL BACKGROUND

2. This Court made extensive findings of fact in *Janssen Pharmaceutica N.V. v. Mylan Pharmaceuticals, Inc.*, 456 F. Supp. 2d 644 (D.N.J. 2006), *aff'd*, 233 Fed. Appx. 999 (Fed. Cir. 2007), a prior patent case involving another antipsychotic drug used to treat schizophrenia. A number of those same findings of fact should be made in this case.

1. Schizophrenia

3. Schizophrenia is a debilitating mental illness that impairs an individual's capacity for thought, attention, memory, emotion, and social functioning. Despite extensive research, the cause of schizophrenia remains unknown. Schizophrenia is viewed as one of the worst mental

³ Plaintiff objects to Defendants including in their contested facts section allegations that were not included in Defendants' expert reports.

illnesses in light of the human suffering it exacts, the lifelong disability it causes, and the lack of adequate treatment. The world-wide prevalence of schizophrenia is about 1%.

4. People with schizophrenia exhibit “positive,” “negative,” and “cognitive” symptoms. The positive symptoms of psychosis include hallucinations, delusions, and thought disorders. Negative symptoms include a loss of social abilities, loss of the ability to fully experience emotions, and other diminutions in normal functions. Cognitive symptoms are characterized by failures of memory, executive function, and attention.

5. The onset of schizophrenia is often sudden and typically occurs in early adult years. Once begun, the illness continues throughout a person’s life, often with little to no improvement. In the early stages of the illness, when symptoms are at their worst, people are often hospitalized for long periods of time. As the illness progresses, individuals with schizophrenia often adopt lifestyles that increase their risk for other illnesses, including heart disease and cancer. The risk of suicide among people with schizophrenia is also high, especially in early adult years.

6. Doctors first attempted to treat schizophrenia in the 1930s and 1940s using fever therapy, adrenalectomy, induction of insulin coma, frontal lobotomy, and electroconvulsive shock therapy. None of these primitive medical procedures were effective.

7. Governments built public hospitals for the mentally ill. By mid-twentieth century, these institutions were near the breaking point, with several thousand patients in a facility that today cares for only a few hundred persons. The term “warehousing” is used to describe treatment in this era.

8. In 1950, no drug treatments for schizophrenia were known, and the cause of the illness remained unknown. The outcome for schizophrenia patients was hopeless, and physicians in the field were discouraged.

2. The First-Generation Antipsychotics

9. The first widely used antipsychotic drug, chlorpromazine, was discovered by accident in the early 1950s. Two French psychiatrists tested chlorpromazine as a pre-anesthetic agent on actively psychotic persons with schizophrenia. During their testing the psychiatrists surprisingly found that the patients' psychotic symptoms improved.

10. Chlorpromazine ushered in a major advance in the treatment of individuals with schizophrenia, allowing for the release of thousands of patients who otherwise would have spent their lives institutionalized. While not curing these patients, chlorpromazine did allow many to engage in relatively normal day-to-day interactions for the first time in years.

11. In the late-1950s, a group led by Paul Janssen of Janssen Pharmaceutica created a more potent antipsychotic called "haloperidol."

12. Chlorpromazine, haloperidol, and similar drugs are known as "first-generation" or "typical" antipsychotics. They share similar potent antipsychotic actions and are effective in reducing many of the positive symptoms of the illness such as hallucinations and delusions. The mechanism of action of these antipsychotics in treating schizophrenia was identified in the 1960s as blockade of dopamine receptors in the brain (also known as the "dopamine hypothesis").

13. Although first-generation antipsychotics emptied out hospitals and provided persons with schizophrenia with some relief from their positive, psychotic symptoms, physicians grew increasingly dissatisfied with these drugs. Two flaws were most prominent. First, residual symptoms were common; these first-generation antipsychotics did not treat negative and cognitive symptoms at all and sometimes even worsened those symptoms. Second, these

antipsychotics produced a number of intolerable side effects including motor side effects such as extrapyramidal symptoms and tardive dyskinesia; elevation of prolactin levels; cardiovascular side effects such as orthostatic hypotension and tachycardia; liver toxicity; and seizures.

14. Extrapyramidal symptoms (“EPS”) are characterized by parkinsonian effects including hypokinesia, rigidity, tremor, masklike facial expression, shuffling gait, and excessive salivation; akathisia (inner restlessness characterized by the inability to remain motionless); and dyskinesias and dystonias (involuntary movements, especially of the face and tongue). EPS, which are often painful, are dose-related and reversible.

15. Even worse, EPS can develop into a more serious motor syndrome called “tardive dyskinesia” (“TD”) characterized by the delayed onset of motor difficulties such as repetitive, involuntary, and purposeless movements. TD frequently continues after the patient has stopped taking medication and may be irreversible or only slowly reversible.

16. Prolactin elevation (hyperprolactinemia) leads to a variety of unpleasant side effects, including breast enlargement in men, galactorrhea (milk production) in women, and osteoporosis (bone wasting).

17. Orthostatic hypotension is a form of sudden decreased blood pressure that may cause a patient to pass out when he or she stands up. Harmful injuries from falls may result. A sudden decrease in blood pressure may even cause older patients to have a stroke or heart attack.

18. The side effects caused by first-generation antipsychotics often led patients to stop taking their antipsychotic medication. This lack of compliance led to relapse of psychotic symptoms and increased hospital stays. It was common for individuals treated with first-generation antipsychotics to experience repeated cycles of hospitalization, discharge, relapse, and rehospitalization over many years.

3. A Second-Generation Antipsychotic: Clozapine

19. Another breakthrough occurred in the mid-1960s with the discovery of clozapine. Clozapine appeared to be effective in treating both the positive and negative symptoms of schizophrenia. Most significantly, however, it was not a “typical” antipsychotic in that it had a much lower propensity to induce EPS. Clozapine was described as the first “second-generation” or “atypical” antipsychotic because it showed that it was possible to separate a drug’s antipsychotic efficacy from its propensity to induce EPS. Unfortunately, clozapine was found in the 1970s to induce a potentially fatal blood disorder called “agranulocytosis” in some patients. Agranulocytosis may cause a patient to die from even minor infections. Clinical trials of clozapine were suspended due to this blood toxicity problem.

20. In 1990, the FDA approved the use of clozapine solely for treatment-resistant schizophrenia patients. Due to the risk of fatal agranulocytosis, patients were required to have regular and costly blood tests to monitor their safety.

4. Failures to Develop Improved Antipsychotics in the 1970s and 1980s

21. With the discovery of the toxicity of clozapine, scientists began searching for compounds that would be safe second-generation antipsychotics. They sought to develop clozapine-like drugs with less toxicity and fewer side effects. The problem was that the cause of schizophrenia remained unknown, and no one knew why clozapine worked the way it did.

22. Scientists made extensive efforts in the 1970s and 1980s to develop improved antipsychotics. Many new chemical compounds were created and tested. Unfortunately, those research efforts largely failed. Most tested compounds lacked antipsychotic activity, were toxic in humans, or had some other unacceptable side effect or property.

23. As a result, the 1970s and 1980s turned out to be a particularly dry period for schizophrenia drug research. In fact, the FDA did not approve a single new antipsychotic drug from about 1976 to 1989.

24. These widespread failures to develop improved antipsychotics were reported in the literature, including, for example, the publications designated as Otsuka's trial exhibits PTX 113 through PTX 289.

25. In *Janssen*, this Court found that it was "undisputed that there was a long-felt but unsolved need for a safe, atypical antipsychotic that did not cause EPS or TD from at least the 1960s until 1985 and beyond." *Janssen*, 456 F. Supp. 2d at 670. This Court further found that researchers in that time period had tried but failed to develop a safe atypical antipsychotic. *Id.* Those findings apply equally to the facts of this case.

26. Pursuant to 35 U.S.C. § 119, the '528 patent is entitled to a priority date of October 31, 1988. As of that date, only first-generation antipsychotics such as chlorpromazine and haloperidol, having the serious shortcomings described above, were available to be prescribed to schizophrenia patients in the United States.

5. The Challenges of Antipsychotic Drug Research

27. There have been many failures in antipsychotic drug discovery because of the complexity and unpredictability of this area of research.

a. Brain Chemistry

28. The human brain is composed of many types of cells, including neurons. Neurons transmit electro-chemical signals within and from the brain. There are about 100 billion neurons in the brain interconnected by hundreds of trillions of synapses. No computer could match the astonishing complexity of the human brain.

29. Neurons communicate with each other and respond to cells elsewhere in the body through signal molecules called “neurotransmitters.” These signal molecules cause changes within brain cells when they bind to specialized “receptors” on the surface of the cell. Receptors are complex structures that interact with particular neurotransmitters to stimulate or modulate a particular physiological response. Much of the effort related to the development of drugs for psychiatric disorders has been directed to finding new molecules, different from the natural transmitter molecules, that bind to and alter the function of receptors in the brain thought to be involved in a particular mental illness.

30. Molecules that bind to a receptor can have two principal effects. They can be “agonists” that stimulate the physiological response of the receptor or “antagonists” that block or prevent the physiological response of the receptor.

31. Many different neurotransmitters activate receptors in the brain, including dopamine, which activates “dopamine” receptors; serotonin, which activates “serotonergic” receptors; histamine, which activates “histaminergic” receptors; norepinephrine, which activates “adrenergic” receptors; and acetylcholine, which activates “cholinergic” (particularly a subtype called “muscarinic”) receptors. In addition, there are numerous subtypes of each of these receptors, e.g., dopamine “D₁” or “D₂” receptors and serotonin “5HT₂” receptors.

b. The Complexity of Antipsychotic Drug Discovery

32. As of the October 31, 1988, priority date, researchers were investigating antipsychotic drug candidates having activity at a variety of receptors in the brain. However, because the cause, mechanism, and etiology of schizophrenia were unknown (and remain so today), it was unknown which of those receptor targets, or combination of receptor targets, was the key to developing an improved second-generation “atypical” antipsychotic. Further, the correct ratio of activity at those various receptors also was unknown (and is unknown today).

Indeed, researchers did not even know why the few successful drugs they were seeking to mimic worked the way they do in humans. All they had was a handful of different and largely unproven hypotheses based on a few known drugs and the corresponding structures of these known drugs as starting points. Consequently, these efforts led to repeated failures.

33. Clozapine was found to have a complex pharmacology, interacting with a variety of different receptors in the brain. Precisely which of those receptors were involved in clozapine's "atypical" therapeutic action and what the optimal balance was between those receptors was unknown in the 1980s and remains unclear today. The discovery of diverse receptor subtypes only further complicated research efforts.

34. The three-dimensional structures of these various receptors were unknown, impeding the design of molecules intended to interact with them. Researchers still have little such information today. The potential need for an antipsychotic to interact with two or more structurally different receptors of unknown structure made the rational design of antipsychotic drugs extremely difficult, if at all possible.

35. Researchers found that modifying the chemical structure of an antipsychotic compound could alter its biological activity in unpredictable ways.

36. Side effects have been a particularly serious problem limiting the development of new antipsychotics. Many promising drugs have failed due to unacceptable side effects.

37. Defendants' various assertions concerning so-called structure-activity relationship ("SAR") analyses are based on speculation and hindsight rather than the actual teachings of the prior art. The prior art provides no SAR information that would have given a person of ordinary skill any reasonable expectation of success or guidance as to how to discover a safe, therapeutically effective atypical antipsychotic such as aripiprazole.

38. Defendants' experts conducted their proposed SAR analyses by starting with the structure of aripiprazole (which is not in the prior art) then working backwards through the alleged prior art, selecting only information that supported their obviousness theories while disregarding all contrary information that would have led away from aripiprazole. This type of hindsight analysis is fatally flawed.

39. Creating an improved antipsychotic drug with a favorable side-effect profile has been an extremely challenging endeavor. Otsuka's aripiprazole is one of only a handful of new antipsychotic drugs that have been developed and approved for marketing since 1975.

6. Otsuka's Discovery of Aripiprazole

40. During the 1980s, Otsuka synthesized hundreds of compounds ("the 4000 series") in the search for a potential atypical antipsychotic. Otsuka chose one of those compounds, "OPC-4392," for advancement to clinical trials in humans during 1984-1986.

41. Unfortunately, a Phase I clinical trial in healthy volunteers indicated that OPC-4392 had potentially serious neurological side effects even at minimal dosages. Even more disappointing, a Phase II clinical trial in schizophrenia patients demonstrated that OPC-4392 did not adequately treat the positive symptoms of schizophrenia and in some cases actually worsened those positive symptoms. Consequently, OPC-4392 never became an approved drug.

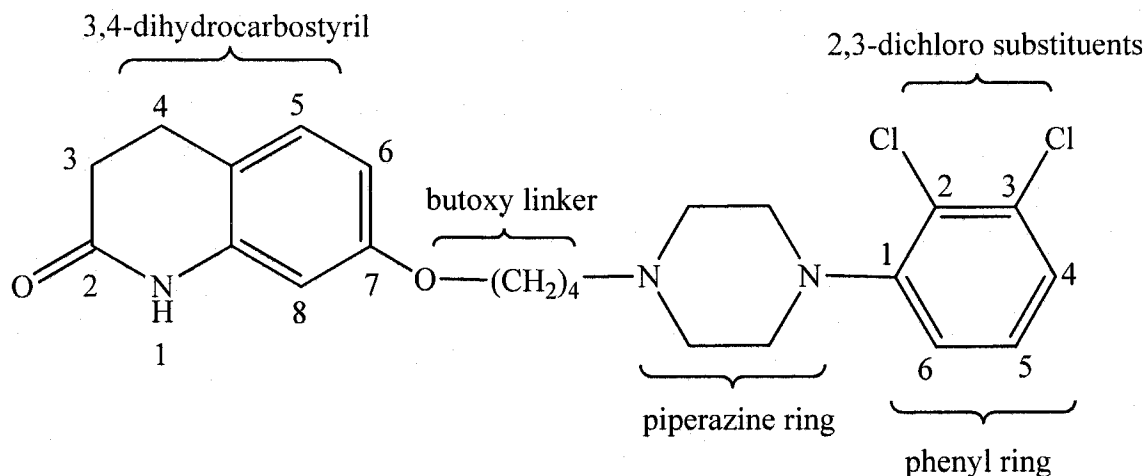
42. Otsuka, however, did not abandon its research. After the unsuccessful clinical trials of OPC-4392, an Otsuka medicinal chemist named Dr. Yasuo Oshiro became involved in the project. He concluded that OPC-4392 failed because Otsuka had used inadequate animal screening methods to identify compounds with potential antipsychotic activity.

43. Dr. Oshiro decided to re-screen Otsuka's 4000 series to identify compounds that could block apomorphine-induced stereotypy in mice ("the stereotypy test"). The stereotypy test is a well-known screen for dopamine receptor blocking activity and, therefore, potential

antipsychotic activity. Dr. Oshiro hoped that using this screening method would assist his team to create a therapeutically effective antipsychotic drug.

44. Dr. Oshiro's team initially identified two 4000 series carbostyryl derivatives that had at least some activity in the stereotypy test. Dr. Oshiro then sought to create other carbostyryl derivatives that were as potent as haloperidol in the stereotypy test. To accomplish this goal, Dr. Oshiro tried a variety of chemical modifications. His efforts led to a new series of compounds referred to within Otsuka as "the 14000 series." Those compounds were then screened for potential antipsychotic activity using the stereotypy test as well as other animal screening tests for potential antipsychotic activity and side effects.

45. Dr. Oshiro's efforts ultimately led to his creation of a novel compound, OPC-14597, now known as "aripiprazole," which is highly potent in the stereotypy test. The chemical structure of aripiprazole is shown below:



Aripiprazole

46. As illustrated, aripiprazole is a carbostyryl derivative in which the following components are joined together to form the molecule: a "3,4-dihydrocarbostyryl" group, a "butoxy" linker, a "piperazine" ring, and a "phenyl" ring with "chlorine" (Cl) substituents at the

2- and 3- positions of the phenyl ring. These features render aripiprazole structurally unique among all known antipsychotics.

47. After further testing in animals, Otsuka advanced aripiprazole to clinical trials in humans. In those trials, aripiprazole was demonstrated to be a safe and therapeutically effective atypical antipsychotic drug.

48. Aripiprazole has a number of therapeutic benefits, including its efficacy in treating the positive symptoms of schizophrenia and favorable side-effect profile, most notably its reduced propensity to cause EPS, TD, sedation, weight gain or other metabolic effects, prolactin elevation, or orthostatic hypotension. Because aripiprazole is a potent antipsychotic having fewer side effects, it is a superior drug for treating psychosis compared to first-generation antipsychotics such as chlorpromazine or haloperidol. In addition, the available clinical evidence suggests that aripiprazole may have better effects on the negative and cognitive symptoms of schizophrenia than first-generation antipsychotics.

49. Aripiprazole is chemically unique as the first and only carbostyryl derivative that has been approved by the FDA as an antipsychotic drug. Aripiprazole is also pharmacologically unique as the first and only FDA-approved antipsychotic drug that is a partial dopamine agonist. Aripiprazole's unique pharmacological properties may help explain its efficacy in treating schizophrenia and favorable side-effect profile.

50. In addition to the treatment of schizophrenia, aripiprazole has been approved (1) as an add-on treatment to antidepressants for major depressive disorders (the first drug approved for that indication), (2) for acute and maintenance treatment of adults with manic or mixed episodes associated with Bipolar I Disorder, (3) for the acute treatment of pediatric patients 10 to

17 years of age with manic or mixed episodes associated with Bipolar I Disorder, and (4) for the treatment of irritability associated with autistic disorder in pediatric patients 6 to 17 years of age.

51. Reflecting its unique clinical properties, U.S. net sales of aripiprazole have totaled more than \$13 billion dollars from 2002 through 2009. In 2009, aripiprazole was the sixth highest selling drug in the United States.

52. Aripiprazole is recognized in the medical community as a major breakthrough. For example, aripiprazole received the Prix Galien (France) award in 2006 for being the most innovative pharmaceutical product on the market. The Prix Galien is considered the most prestigious pharmaceutical industry award. Aripiprazole has received many other honors and awards.

7. Otsuka's Patenting of Aripiprazole and Related Compounds

53. Otsuka sought patent protection for aripiprazole and certain related compounds by filing in the PTO the '719 application, which later issued as the '528 patent. The '719 application was filed on October 20, 1989, and included a claim to priority to an earlier filed Japanese application, filed October 31, 1988.

54. The '719 application was thoroughly examined during the original prosecution by PTO Examiner Turnipseed, who was familiar with the prior art, having previously examined multiple patent applications concerning carbostyryl compounds. During this original prosecution, Examiner Turnipseed conducted a careful search of the relevant prior art, including searches of the PTO's hard copy document collections as well as electronic databases, and then explicitly considered the patentability of the claims of the '719 application in light of U.S. Patent No. 4,824,840 ("the '840 patent"), a prior Otsuka patent, also previously examined by Examiner Turnipseed. The '840 patent discloses a broad genus of carbostyryl compounds and about 500 specific carbostyryl derivatives, including the so-called "unsubstituted butoxy" compound

Defendants now rely upon in their obviousness defense. The PTO ultimately concluded that the patent claims were patentable in light of that prior art.

55. The '528 patent was then examined a second time by the PTO during a reexamination proceeding initiated by Otsuka. During the reexamination proceedings, the PTO considered dozens of references, including those disclosing the compounds Defendants identify as the most relevant prior art. After reviewing this information, a group of three experienced PTO Examiners again confirmed the patentability of claims 1-21 of the '528 patent and also determined that additional claims 22-24 were patentable as well.

56. The '528 patent currently expires on April 20, 2015, including a six-month period of pediatric exclusivity.

8. Otsuka's Approved Aripiprazole Formulations

57. As discussed above in the Stipulated Facts, Otsuka received FDA approval of its NDA No. 21-436 in 2002, allowing the marketing of aripiprazole tablets in the United States as an antipsychotic for the treatment of schizophrenia. Otsuka, with its partner Bristol-Myers Squibb, began marketing aripiprazole in 2002 under the name Abilify®.

58. Otsuka is also the holder of NDA No. 21-729 for orally disintegrating tablets containing aripiprazole, which the FDA approved on June 7, 2006. Otsuka lists the '528 patent in the Orange Book for NDA No. 21-729. Active Defendant Barr and stayed Defendant Zydus seek approval to market infringing generic aripiprazole orally disintegrating tablet formulations and these products are therefore also at issue in these consolidated litigations.

59. Otsuka markets its aripiprazole tablet and orally disintegrating tablet formulations that are the subjects of NDA Nos. 21-436 and 21-729 under the trade name Abilify®.

60. In addition to NDA Nos. 21-436 and 21-729, Otsuka is also the holder of NDA Nos. 21-713 and 21-866 for oral solution and injectable formulations containing aripiprazole, respectively. Otsuka lists the '528 patent in the Orange Book for these NDAs. The oral solution and injectable formulations of aripiprazole are not at issue in the actions currently set for trial. Otsuka has filed two actions against Teva concerning aripiprazole oral solution products, but the parties have agreed to stay those actions and to be bound by the final judgment in the present action regarding the validity and enforceability of the '528 patent. *See* Civil Action No. 07-cv-01000 (MLC) at D.I. 123 and Civil Action No. 09-cv-05531 at D.I. 5. Otsuka is unaware of any ANDA directed to an injectable aripiprazole formulation.

B. THE '528 PATENT IS VALID

1. Defendants' Obviousness Defense Lacks Merit

61. A finding of obviousness requires an analysis of: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) whether those differences are such that the claimed invention as a whole would have been obvious to a person having ordinary skill at the time the invention was made. Secondary considerations of nonobviousness also must be considered. All of these factors weigh in favor of a determination of nonobviousness with respect to the asserted claims of the '528 patent.

62. Each of claims 12, 17, and 23 of the '528 patent recites, as a limitation, the compound aripiprazole described by its chemical name: 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydrocarbostyryl. Claim 17 further specifies a pharmaceutical composition containing aripiprazole for the treatment of schizophrenia, and claim 23 specifies a method of treating schizophrenia by administering a pharmaceutical composition containing aripiprazole. As depicted in the chemical drawing above, aripiprazole is a carbostyryl derivative

that includes, in a specific configuration, a 3,4-dihydrocarbostyryl group, a butoxy linker, a piperazine ring, and a phenyl ring with chlorine substituents at the 2- and 3- positions of the phenyl ring.

63. Defendants do not contend that aripiprazole is described anywhere in the prior art. Instead, using legally improper “hindsight” analysis, Defendants argue that a person of ordinary skill in October 1988 would have selected one particular carbostyryl derivative (which they refer to as “the unsubstituted butoxy compound”) as a starting or “lead” compound from among hundreds of other carbostyryl derivatives described in the prior art, allegedly knowing that it would have antipsychotic activity, then would have been motivated to modify that compound by adding chlorine substituents at both the 2- and 3- positions of the phenyl group to arrive at aripiprazole. This defense is factually unsupported for several reasons.

a. A Person of Ordinary Skill Would Not Have Selected Any Carbostyryl Derivative as a Lead Compound for Antipsychotic Drug Development

64. A person of ordinary skill in the art in October 1988 would have had a master’s degree in chemistry, medicinal chemistry, or pharmacy, or a bachelor’s degree in one of those fields with at least two years of experience in antipsychotic drug research. *See Janssen*, 456 F. Supp. 2d at 654. Contrary to Defendants’ contention, a person of ordinary skill in the art would not have been a multidisciplinary team of medicinal chemists and pharmacologists led by someone with a Ph.D. or an M.D. Neither would a person of ordinary skill have been a scientist having a Ph.D. and several years of experience studying antipsychotic drugs. Such a person would be of *extra* ordinary skill, not ordinary skill. Yet, even if a higher level of ordinary skill applies, as proposed by Defendants, the asserted claims of the ’528 patent still would not have been obvious.

i. OPC-4392 Failed in Clinical Trials

65. A person of ordinary skill in October 1988 would not have selected any carbostyryl derivative as a lead compound for development because no carbostyryl derivative had ever been shown by 1988 to adequately treat the positive symptoms of schizophrenia. To the contrary, the only carbostyryl derivative that had even been tested in humans as a potential antipsychotic, OPC-4392, failed because it did not effectively treat the positive symptoms of schizophrenia, as reported in publications of the Phase II clinical studies.

66. In addition, a Phase I study published in March 1988 suggested that OPC-4392 had potentially serious side effects in healthy volunteers, even at the low doses tested, including “stagger, weakness, fatigability, heavy headedness, lack of motivation and disturbed concentration, which were so severe that they were not able to perform daily routine work” and “mental anguish to perform daily routine work.” An antipsychotic medication is intended to improve the mental state of a schizophrenia patient, not cause “mental anguish” or other severe neurological side effects. The potentially serious side effects reported in the Phase I study, coupled with the lack of efficacy reported in the Phase II study, would have eliminated any possible interest in OPC-4392 or any other carbostyryl derivative as a potential lead compound.

67. The clinical failure of OPC-4392 will be explained at trial by Otsuka’s experts Dr. Carol Tamminga and Dr. Bryan Roth, who are both medical doctors with many years of experience in evaluating clinical trials of potential antipsychotic drugs. Defendants’ experts are not medical doctors and have no experience or expertise in evaluating the results of clinical trials of antipsychotic drugs in human patients. Thus, Defendants will be unable to dispute that the clinical trials of OPC-4392 were unsuccessful.

68. One of ordinary skill in the art would likewise have had no interest in OPC-4139, another carbostyryl compound identified by Defendants. Otsuka abandoned any plans to develop

this compound in favor of OPC-4392, which subsequently failed in clinical trials as explained above. Moreover, OPC-4139 was reported to have no activity in the stereotypy test, the test Otsuka used to discover aripiprazole.

ii. Derivatives of Known Antipsychotics Would Have Appeared Far More Promising as Lead Compounds Than Any Carbostyryl Derivative

69. Reflecting their hindsight approach, Defendants begin and end their obviousness analysis with carbostyryl derivatives, failing to even consider any other types of compounds that a person of ordinary skill would have investigated in 1988 as potential atypical antipsychotics.

70. The scope and content of the prior art as of October 31, 1988, provided no clear guidance as to how to discover a new antipsychotic drug. The cause of schizophrenia was unknown, and antipsychotic drug discovery was highly unpredictable.

71. Researchers in the 1980s sought to discover clozapine-like antipsychotics with reduced adverse effects (e.g., no agranulocytosis). They modified the structure of clozapine in an effort to remove the drug's adverse effects while maintaining its efficacy in treating schizophrenia without EPS. Many clozapine derivatives were created as potential antipsychotics, two of which eventually became FDA-approved antipsychotic drugs. A person of ordinary skill in 1988 therefore most likely would have selected a derivative of clozapine as a lead compound for antipsychotic drug development rather than any carbostyryl derivative.

72. This Court found in *Janssen* that a person of ordinary skill in 1985 would have selected clozapine (or another known antipsychotic, thioridazine) as a lead compound for antipsychotic drug development. *Janssen*, 456 F. Supp. 2d at 662. This Court certainly did not find that a person of ordinary skill would have selected a lead compound from an entirely unproven class of compounds such as the carbostyryl derivatives. Further, although *Janssen*

involved a 1985 priority date rather than 1988, clozapine remained a primary target of schizophrenia researchers in 1988.

73. In addition to clozapine, a person of ordinary skill could have selected a derivative of risperidone as a lead compound for antipsychotic drug development. Risperidone was emerging from clinical trials by 1988 as a promising antipsychotic that could treat schizophrenia with lower EPS. Two other risperidone-like compounds subsequently gained FDA approval as antipsychotic drugs.

74. Notably, except for Otsuka's structurally unique aripiprazole, all new antipsychotics to gain FDA approval since 1975 have been similar to either clozapine or risperidone. This fact confirms that a person of ordinary skill in 1988 would have been led towards a derivative of clozapine or risperidone as a lead compound, not any carbostyryl derivative.

75. Because OPC-4392 lacked antipsychotic efficacy and had potentially serious side effects, and derivatives of known antipsychotics such as clozapine or risperidone appeared far more promising for antipsychotic drug development, a person of ordinary skill in 1988 would have been led away from, not toward, carbostyryl derivatives as potential antipsychotics. Consequently, the entire premise of Defendants' obviousness defense—that a person of ordinary skill seeking to develop an improved antipsychotic would have started with a carbostyryl derivative—is factually unsupported.

b. A Person of Ordinary Skill Would Not Have Selected the Unsubstituted Butoxy Compound as a Lead Compound for Antipsychotic Drug Development

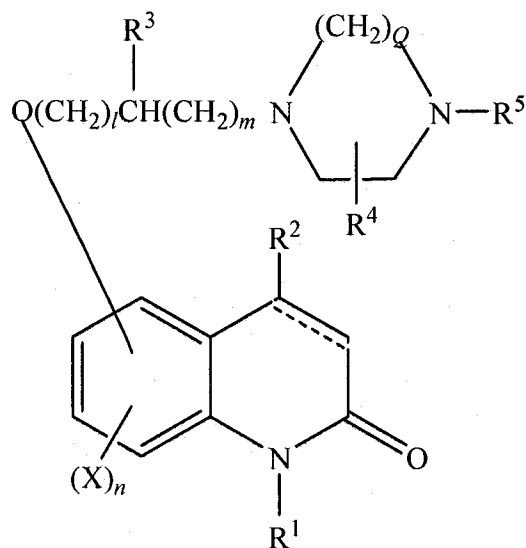
76. Even if a person of ordinary skill in 1988 would have been interested in carbostyryl derivatives as potential antipsychotics, nothing in the prior art points to the

unsubstituted butoxy compound as a promising lead compound. To the contrary, the prior art teaches away from it.

i. The '416 Patent Teaches Away from the Unsubstituted Butoxy Compound

77. Defendants rely primarily on the '416 patent, entitled "Pharmaceutically Useful Carbostyryl Derivatives." The PTO confirmed the patentability of the claims of the '528 patent over the '416 patent during the reexamination proceeding. In addition, during both the original prosecution and reexamination of the '528 patent, the PTO found the claims patentable over a related patent (the '840 patent) that discloses the same carbostyryl derivatives as the '416 patent. Defendants' reliance on prior art that was already fully considered by the PTO highlights the weakness of their arguments.

78. The '416 patent describes an enormously broad group of carbostyryl derivatives represented by the formula (1) shown below:



79. Formula (1) allows broad variation in the substituents R^1 , R^2 , R^3 , R^4 , R^5 , and X , in the numbers l and m of methylene units (CH_2) in the alkoxy linker, in the number n of substituents X , in the positions of attachment of the alkoxy linker and the $(X)_n$ substituents on the

bicyclic carbostyryl or 3,4-dihydrocarbostyryl ring system, and in the size Q and position of substitution by R^4 of the saturated ring containing two nitrogen atoms. In view of this broad variation, formula (1) encompasses many billions of different chemical structures.

80. The '416 patent also identifies by name about 250 specific carbostyryl derivatives (none of which is aripiprazole) and indicates that each of those compounds may exist in two forms, resulting in a total of about 500 specifically named carbostyryl derivatives. One of those 500 carbostyryl derivatives is the unsubstituted butoxy compound, which the '416 patent identifies by its chemical name "7-[4-(4-Phenylpiperazinyl)butoxy]-3,4-dihydrocarbostyryl." The '416 patent does not specifically disclose or claim OPC-4392 despite Defendants' suggestions to the contrary.

81. No preferences are stated among the 500 compounds listed in the '416 patent, and no information is provided that could have led a person of ordinary skill to pick out the unsubstituted butoxy compound from those listed compounds.

82. The examples of the '416 patent describe about 100 carbostyryl derivatives, which vary widely in their structures consistent with the broad variation permitted by formula (1).

83. The '416 patent contains no experimental data relating to potential antipsychotic activity. The patent only describes test data relating to potential antihistaminic activity; anesthesia and sleep increasing activity; sedative, anxiolytic, and anti-manic depressive activity; analgetic activity; and acute toxicity. A person of ordinary skill therefore would have interpreted the '416 patent as being primarily directed to compounds that may have antihistaminic, sedative, antianxiety, or other pharmacological activities unrelated to antipsychotic activity.

84. The '416 patent contains a passing reference to "antischizophrenia agents" in a list of other potential uses, i.e., "central muscle relaxing agents, sleep-inducing agents, pre-

operative drugs, antischizophrenia agents, sedatives, antianxiety drugs, anti-manic depressive psychosis agents, antipyretic agents, analgetic agents and depressors”

85. Defendants suggest that a person of ordinary skill would have selected the unsubstituted butoxy compound as a lead compound because it is recited in claim 13 of the '416 patent. There are 118 claims in the '416 patent, however, so there would have been no reason to focus on claim 13. Further, there are 60 specifically claimed compounds in the '416 patent encompassing many different chemical structures. Looking at all the claims (rather than singling out claim 13 through hindsight), there would have been no reason to select the unsubstituted butoxy compound as a lead compound rather than one of the 59 other specifically claimed compounds.

86. Defendants overlook the critical fact that the unsubstituted butoxy compound is also specifically claimed in claim 116 of the '416 patent. Unlike claim 13, which does not identify any use for the unsubstituted butoxy compound, claim 116 recites a specific use for that compound. In particular, claim 116 depends from claim 50, which recites a “method for producing an antihistaminic effect.” Claim 116 therefore expressly indicates that the unsubstituted butoxy compound is an antihistamine. A person of ordinary skill would not have selected an antihistamine as a lead compound for antipsychotic drug development.

87. Certain claims of the '416 patent focus on compounds intended to produce “a central nervous controlling effect”; however, those claims do not include the unsubstituted butoxy compound within their scope.

88. The '416 patent therefore describes the unsubstituted butoxy compound as an antihistamine and teaches away from its use as an antipsychotic.

89. Defendants have no evidence that a person of ordinary skill in the art would have selected an antihistamine as a lead compound in the search for a potential antipsychotic.

90. Defendants also cite certain European counterpart patents related to the '416 patent, but those patents similarly fail to describe the unsubstituted butoxy as an antipsychotic or otherwise suggest that it would be a suitable lead compound for antipsychotic drug development.

ii. The Nakagawa Declaration Teaches Away from the Unsubstituted Butoxy Compound

91. Defendants also cite a declaration of Dr. Kazuyuki Nakagawa ("the Nakagawa declaration") filed by Otsuka during prosecution of the '416 patent as allegedly suggesting the selection of the unsubstituted butoxy as a lead compound. The Nakagawa declaration, however, is not prior art to the '528 patent and is therefore irrelevant to alleged obviousness.

92. Even if the Nakagawa declaration were prior art, it would not support Defendants' flawed obviousness defense.

93. The Nakagawa declaration reports the testing of compounds for activity in inhibiting the jumping behavior of mice induced by methamphetamine and L-DOPA ("the mouse jumping test"). The mouse jumping test is significantly different than the stereotypy test that Otsuka used to discover aripiprazole. The mouse jumping test is not indicative of postsynaptic D₂ receptor antagonism. Moreover, unlike the stereotypy test, there is no evidence that the mouse jumping test has ever been used successfully to identify any new antipsychotic drug. A person of ordinary skill seeking to make an improved antipsychotic would have given little or no weight to the mouse jumping test data reported in the declaration.

94. Even if the mouse jumping test would have been viewed as a screen for antipsychotic activity, a person of ordinary skill would have selected the compound that most potently inhibited mouse jumping. Potent compounds are desirable because they reduce the

therapeutic dose, which minimizes the risk of off-target activity and side effects. The two most potent compounds in the Nakagawa declaration (5-isomer compounds "44" and "5") differ significantly from the unsubstituted butoxy compound. Therefore, the Nakagawa declaration teaches toward compounds having the structural features of those compounds and away from the much less potent unsubstituted butoxy compound.

95. Defendants incorrectly argue that a person of ordinary skill would have disregarded compounds 44 and 5 because 5-isomer compounds allegedly have cardiovascular side effects. There is no factual basis for this assertion. A person of ordinary skill would not have disregarded the most potent compounds of the Nakagawa declaration (the 5-isomer carbostyrils).

96. Defendants also argue that a person of ordinary skill would have selected 7-position carbostyril derivatives over the more potent 5-position carbostyril derivatives because OPC-4392 was a 7-position compound and the only carbostyril tested in clinical trials. Defendants select only one structural feature of OPC-4392 -- the 7-position isomer, while ignoring others that do not support their opinions. For example, they ignore the facts that OPC-4392 was a dimethyl substituted compound containing a propoxy linker. If a person of ordinary skill would have been so interested in OPC-4392, as Defendants contend, such person would have been interested in the 2,3-dimethyl substitution, the propoxy linker, and the carbostyril ring structure, not just the 7-position of the carbostyril core. Defendants, however, simply disregard the structural features of OPC-4392 that are unhelpful to their allegations.

97. Defendants also disregard what happened to OPC-4392 *after* it was "selected" as a clinical candidate, namely, that OPC-4392 was clinically tested in humans and found to be "not strong" as an antipsychotic. In reality, a person of ordinary skill aware of the reported

inadequacy of OPC-4392 to treat the positive symptoms of schizophrenia effectively would have abandoned plans to research other carbostyryl derivatives. Even if such a person of ordinary skill would not have abandoned all research on carbostyryls, however, the poor clinical results for OPC-4392 would have even more strongly directed such a person to select the most potent compounds of the Nakagawa declaration (the 5-position isomers) for further study.

98. Even improperly disregarding the 5-isomers, two other tested compounds, both propoxy-linked compounds, were more potent than the unsubstituted butoxy compound. A person of ordinary skill would have selected one of those compounds over the unsubstituted butoxy compound. Both of those compounds differ significantly from the unsubstituted butoxy compound.

99. Ignoring these most potent compounds, Defendants rely on an alleged head-to-head comparison between the unsubstituted propoxy compound and the unsubstituted butoxy compound. There is no such head-to-head comparison; the Nakagawa declaration contains test results for eight propoxy compounds and one butoxy compound. Defendants disregard that eight of the nine compounds tested in the declaration are propoxy-linked compounds and the fact that, if anything, the Nakagawa declaration teaches a clear preference for propoxy-linked compounds, not butoxy-linked compounds.

100. Defendants further disregard the fact that there were published prior art patents disclosing mouse jumping test results for other carbostyryl and isocarbostyryl derivatives that differed significantly in structure compared to the unsubstituted butoxy compound. Defendants have no evidence that a person of ordinary skill in 1988 would have disregarded those other prior art carbostyryl or isocarbostyryl derivatives in favor of the unsubstituted butoxy compound. Defendants' argument that one of skill in the art would have ignored these compounds because

of alleged cardiovascular side effects is unsupported and is at odds with the teachings of these patents. Moreover, Defendants argument that one of skill in the art would ignore these compounds in light of the later alleged work by Otsuka with respect to OPC 4392 and the compounds in the Nakagawa declaration has the chronology exactly backwards. The compounds in these other patents disclosing mouse jumping data were discovered and patented *after* OPC 4392 and the compounds included in the Nakagawa declaration.

101. Finally, even if the Nakagawa declaration were prior art, a person of ordinary skill would have considered the prosecution history of the '416 patent as a whole, not just the Nakagawa declaration in isolation. A person of ordinary skill would have found that the prosecution history of the '416 patent teaches away from selecting the unsubstituted butoxy as a lead compound for antipsychotic drug development.

102. The Nakagawa declaration therefore provides no basis for a person of ordinary skill to select the unsubstituted butoxy compound as a lead compound and in fact teaches away from the subject matter of claims 12, 17, and 23 of the '528 patent.

c. The Prior Art Fails to Suggest Modifying the Unsubstituted Butoxy Compound to Obtain Aripiprazole

103. Even assuming incorrectly that a person of ordinary skill in 1988 would have been interested in carbostyryl derivatives as potential antipsychotics, and also assuming incorrectly that such a person somehow would have selected the unsubstituted butoxy compound as a lead compound rather than one of the hundreds of other specifically identified carbostyryl derivatives in the prior art, there still is no prior art teaching that would have led such a person to modify the structure of the unsubstituted butoxy compound to obtain aripiprazole.

104. There are thousands of ways that the unsubstituted butoxy compound could have been modified. Only one particular combination of structural modifications (substituting

chlorine substituents at both the 2- and 3- positions of the phenyl group) would have led to aripiprazole. No prior art, however, suggests making those or any other modifications to the unsubstituted butoxy compound. Given the high level of unpredictability of antipsychotic drug research, there would have been no reasonable expectation of success with respect to any potential modification of this compound.

105. Defendants identify no prior art suggesting that the unsubstituted butoxy compound should be modified in any way. Lacking prior art, Defendants resort to generalities and speculation. Defendants assert, for example, that chlorine substitution is often the first substitution tried in central nervous system (“CNS”) drug development. That is an overly broad generalization. In particular drug development efforts, a medicinal chemist may first try various substituents other than chlorine, may avoid adding any chlorine, or may avoid any substituents at all.

106. Defendants speculate that chlorination may increase a compound’s lipophilicity, leading to greater penetration through the blood-brain barrier (“BBB”). Chlorination, however, could have the opposite effect with respect to penetrating the BBB. Moreover, there is no evidence that carbostyryl derivatives lack lipophilicity or have any difficulty penetrating the BBB. A person of ordinary skill therefore would not have been motivated to chlorinate the unsubstituted butoxy compound to enhance its penetration through the BBB.

107. Defendants identify only a handful of CNS drugs that include a chlorine substituent. Many antipsychotic drugs, however, lack any chlorine substituent, including risperidone, thioridazine, and numerous others. Because many clinically effective antipsychotics lack any chlorine substituent, a person of ordinary skill would not have believed that chlorine substitution is necessary for antipsychotic activity.

108. Even if it were common for antipsychotics to include a single chlorine substituent, Defendants fail to identify any known antipsychotic in 1988 that was a 2,3-dichloro substituted compound like aripiprazole. In fact, aripiprazole appears to be the only antipsychotic drug with a 2,3-dichloro substituted phenyl group that has ever been approved by the FDA. Because 2,3-dichloro substituted antipsychotics were unknown in 1988, it would not have been obvious to make an antipsychotic with a 2,3-dichloro substituted phenyl group.

109. The Nakagawa declaration, even if considered as prior art, also provides no basis for a person of ordinary skill in the art to modify the unsubstituted butoxy compound to arrive at aripiprazole with a reasonable expectation of success. The Nakagawa declaration lists compounds that are either unsubstituted or monosubstituted on the phenyl ring. Thus, the Nakagawa declaration teaches away from disubstituted compounds like aripiprazole. Moreover, one of ordinary skill in the art would have had no expectation that the effects of various substitutions would be additive. Defendants' assertions to the contrary are based on hindsight.

110. Finally, the 2,3-dichloro propoxy compound (Example 317) of DE '105 and Swedish Patent Application No. 434,945 likewise provides no motivation to modify the unsubstituted butoxy compound to arrive at aripiprazole with a reasonable expectation of success. The DE '105 and related foreign patents simply list the unsubstituted butoxy compound and the 2,3-dichloro propoxy compound among hundreds of other specifically named compounds. They do not suggest the combination of any features of these specific compounds. Nor do these patents provide any reasonable expectation of success from any such combination.

d. Defendants' Alternative Theory of Obviousness Also Lacks Merit

111. Relying on a second team of expert witnesses hired by defendant Apotex, Defendants present an alternative theory of alleged obviousness, arguing that it would have been

obvious in 1988 to start from Otsuka's OPC-4392 compound and modify it to arrive at aripiprazole. This position is factually unsupported.

112. Because OPC-4392 failed in clinical trials, a person of ordinary skill would not have selected it as a lead compound. Rather, a person of ordinary skill would have started with a derivative of clozapine, risperidone, or another known antipsychotic.

113. A person of ordinary skill would have had no idea how to convert OPC-4392 from a failed compound to a safe, therapeutically effective antipsychotic. Nothing in the prior art suggests how one could modify OPC-4392 to convert it to a useful antipsychotic drug.

114. The Nakagawa declaration, even if considered as prior art, provides no basis for a person of ordinary skill in the art to modify OPC-4392 to arrive at aripiprazole with a reasonable expectation of success. Defendants' assertions to the contrary are based on hindsight.

115. The so-called "Wise poster" cited by Defendants is not prior art, concerns "coumarins" rather than carbostyryl derivatives, and teaches away from the invention of the '528 patent. Nothing in the Wise poster refers to any carbostyryl derivative or in any way suggests modifying OPC-4392, or in any way indicates that the coumarins therein are any more pertinent than any other compound, including other Wise compounds.

116. Moreover, even if Wise's work on coumarins had any relevance to carbostyryl compounds, the Wise poster does not suggest the use of a butoxy linker in either coumarins or carbostyryls, as Defendants contend. The Wise poster in fact identifies a propoxy-linked compound, PD-116795, as the key and most promising antipsychotic compound, thus teaching a preference for that linking group. The Wise poster also notes that the tested coumarin compounds lost all activity upon substitution of the phenyl ring, thus further teaching away from the structural features of aripiprazole, which has a disubstituted phenyl ring.

117. If a person of ordinary skill in the art would have been interested in Wise's work on coumarins, as Defendants contend, such person would have been interested in the coumarin core, not just the butoxy linker.

118. The pharmacological tests, including the spontaneous locomotor test, described in the Wise poster bear no relation to the stereotypy test used by Otsuka to discover aripiprazole. Moreover, the spontaneous locomotor test is not a specific test for D₂ dopamine receptor antagonism and cannot be directly associated with antipsychotic activity. Many compounds lacking any antipsychotic properties give false positive results in the spontaneous locomotor test.

119. U.S. Patent No. 4,701,456 ("the '456 patent") would not have led a person of ordinary skill to aripiprazole, as Defendants contend. The '456 patent discloses a broad genus of coumarin compounds, not carbostyrils; provides no basis for a person of ordinary skill in the art to modify OPC-4392 to arrive at aripiprazole with a reasonable expectation of success; teaches a strong preference towards coumarins with a propoxy linker; and teaches away from aripiprazole. For example, pharmacological test data are provided for only two coumarin compounds with a phenyl piperazine group, both of which are propoxy-linked and are unsubstituted at the phenyl group. Moreover, the pharmacological tests described in the '456 patent bear no relation to the stereotypy test used by Otsuka to discover aripiprazole.

120. To arrive at aripiprazole from OPC-4392, a person of ordinary skill would have had to (1) change OPC-4392's methyl substituent at the 2- position of the phenyl group to a chloro substituent, (2) change OPC-4392's methyl substituent at the 3- position of the phenyl group to a chloro substituent, (3) change OPC-4392's propoxy linker to a butoxy linker, and (4) change OPC-4392's carbostyryl nucleus to a dihydrocarbostyryl nucleus—all while disregarding the thousands of other ways that OPC-4392 could be modified. The prior art, however, fails to

suggest making any changes to OPC-4392, much less making the specific molecular changes needed to create aripiprazole.

121. The prior art likewise provides no reasonable expectation of success with respect to any specific structural modification of OPC-4392.

122. Defendants' alternative obviousness position is based on hindsight and speculation rather than the actual teachings of the prior art.

e. Objective Evidence Independently Establishes that Aripiprazole Would Not Have Been Obvious

123. Defendants cannot establish a *prima facie* case of obviousness. Even if they could, there is overwhelming objective evidence of nonobviousness, including evidence of long-felt but unmet need, failures of others, commercial success, copying, unexpected results, and industry acclaim.

i. Long-Felt But Unmet Need

124. As of 1988, there was a long-standing medical need for an improved antipsychotic drug that could treat the positive symptoms of schizophrenia with reduced side effects. All antipsychotics marketed in the United States in 1988 were first-generation antipsychotics such as haloperidol and chlorpromazine, which treated the positive symptoms of schizophrenia but still caused serious side effects such as EPS and TD. The second-generation antipsychotics Defendants point to in an effort to challenge Otsuka's evidence of long-felt need were not available to patients in October 1988, the relevant date for assessing long-felt need.

125. Because schizophrenia is a heterogeneous disorder, which exhibits a variety of symptoms and varying patient responses to treatments, there also was a need in 1988 for a new antipsychotic medication with a unique pharmacological profile, such as aripiprazole.

126. As this Court previously found, it is “undisputed that there was a long-felt but unsolved need for a safe, atypical antipsychotic that did not cause EPS or TD from at least the 1960s until 1985 and beyond.” *Janssen*, 456 F. Supp. 2d at 670. Aripiprazole met that long-felt but unmet need for a safe and effective antipsychotic with reduced side effects.

ii. Failures of Others

127. Researchers attempted for years to create an improved antipsychotic that would treat the positive symptoms of schizophrenia without causing EPS, TD, or other adverse effects such as agranulocytosis. Those efforts largely failed, as reflected, for example, by the fact that the FDA did not approve a single new antipsychotic drug from about 1976 to 1989. *See also Janssen*, 456 F. Supp. 2d at 670 (finding that there was a failure to develop a safe atypical antipsychotic). These widespread failures further establish that aripiprazole would not have been obvious.

iii. Commercial Success

128. Aripiprazole has been widely prescribed by physicians in the United States for treatment of schizophrenia since 2002. Thousands of patients suffering from schizophrenia and other debilitating mental disorders have benefited from this new drug.

129. Physicians prescribe aripiprazole for its significant therapeutic benefits, including its efficacy in treating the positive symptoms of schizophrenia and favorable side-effect profile. Aripiprazole’s unique pharmacological profile and significant therapeutic benefits drive the demand for aripiprazole, not any of the extraneous factors offered by the Defendants.

130. Aripiprazole has been commercially successful as an antipsychotic drug for the treatment for schizophrenia. Aripiprazole also has been commercially successful as an approved drug for the treatment of other mental disorders. Aripiprazole has been successful relative to other atypical antipsychotic drugs with respect to both sales and growth of market share.

131. Since its launch as a drug in 2002, U.S. sales of aripiprazole have exceeded \$13 billion. Achieving “blockbuster” status, U.S. sales of aripiprazole have exceeded \$1 billion for multiple years in a row. In 2009 alone, U.S. net sales exceeded \$3 billion, making aripiprazole the sixth highest selling drug in the United States. There is a nexus between that commercial success and the claimed invention, aripiprazole. Aripiprazole’s tremendous commercial success further establishes that it was an unobvious medical advance.

132. Aripiprazole has achieved tremendous success relative to that of its atypical antipsychotic competitors with respect to both sales and growth of market share.

133. Defendants’ challenge to the commercial success of aripiprazole based on Otsuka’s “blocking” patent position is unsupported. There is no evidence that any competitor refrained from developing aripiprazole or other carbostyryl derivatives due to concerns about any “blocking” patent owned by Otsuka. Moreover, having chosen not to engage an economics expert, Defendants will be unable to offer any expert testimony concerning this speculative theory or any other attempted rebuttals to Otsuka’s commercial success evidence.

134. Defendants’ remaining challenges to the commercial success of aripiprazole are likewise without merit and rely on a misstatement of patent law. All of aripiprazole’s commercial success is properly linked to Otsuka’s discovery of aripiprazole.

iv. Copying

135. Defendants seek to market exact generic copies of aripiprazole, the compound covered by claim 12 of the ’528 patent. All actively participating Defendants have stipulated to infringement of the asserted claims. Defendants’ copying of aripiprazole is evidence of nonobviousness. *See Janssen*, 456 F. Supp. 2d at 671 (finding that copying of antipsychotic drug risperidone by generic drug company ANDA filers was evidence of nonobviousness).

136. Defendants also have copied aripiprazole in the filing of their own patent applications relating to aripiprazole, which Defendants have pursued in the United States and numerous other countries around the world. Defendants' contention that certain aspects of their extensive copying of aripiprazole may not be contrary to U.S. law, even if true, does not negate the fact that Defendants have copied Otsuka's inventions.

v. Unexpected Results

137. Aripiprazole has a number of unexpected therapeutic benefits as a partial dopamine agonist, including its broad efficacy in treating the positive symptoms of schizophrenia and favorable side-effect profile, e.g., causing reduced or no EPS, TD, sedation, weight gain or other metabolic effects, prolactin elevation, or orthostatic hypotension. The drug's therapeutic benefits and side-effect profile could not have been predicted in 1988.

138. Aripiprazole exhibits unexpectedly greater potency in the stereotypy test than prior art carbostyryl derivatives (including the unsubstituted butoxy compound and OPC-4392), consistent with the fact that it is the only carbostyryl derivative that has been shown to be a therapeutically effective antipsychotic.

139. Aripiprazole has been approved for several other indications, including as an add-on treatment for major depressive disorders, for acute and maintenance treatment of adults with manic or mixed episodes associated with Bipolar I Disorder, for the acute treatment of pediatric patients 10 to 17 years of age with manic or mixed episodes associated with Bipolar I Disorder, and for the treatment of irritability associated with autistic disorder in pediatric patients 6 to 17 years of age. Aripiprazole's efficacy in treating those medical conditions would have been completely unexpected to a person of ordinary skill in 1988.

vi. Industry Acclaim

140. The medical community views aripiprazole as a breakthrough based on its ability to treat the positive symptoms of schizophrenia while maintaining a favorable side-effect profile. Aripiprazole received the prestigious Prix Galien (France) award in 2006 for being the most innovative pharmaceutical product on the market. Aripiprazole has received many other honors and awards.

141. For all these reasons, Defendants will be unable to prove that the asserted claims of the '528 patent are invalid for obviousness.

f. Defendants' Remaining Obviousness Allegations Also Lack Merit

142. In addition to the specific arguments addressed above, Defendants offer various vague allegations in alleged support of their obviousness arguments. These arguments also fail for many of the same reasons discussed above.

143. Defendants list in their contested facts multiple alleged prior art publications which they suggest, without any explanation, are relevant to their obviousness allegations. These publications are either not prior art, are cumulative to the references discussed above which do not render the claims obvious, or are simply irrelevant to any obviousness analysis.

144. Defendants point out that the claims of the '416 patent cover a broad genus of carbostyryl compounds including aripiprazole and that Otsuka previously listed the '416 patent in the Orange Book with respect to aripiprazole. Defendants do not explain how these facts are relevant to their obviousness arguments and, indeed, they are not.

145. Contrary to Defendants' assertion, the prior art does not "bracket" aripiprazole. This hindsight-driven approach has no application in an assessment of alleged obviousness. The prior art does not suggest pairing the compound of Example 317 and the unsubstituted butoxy compound as a "bracket." Moreover, there are innumerable alternative combinations of

carbostyryl derivatives in the prior art that would have “bracketed” other equally unknown and untested compounds.

146. Given the unpredictability in antipsychotic drug discovery, a person of ordinary skill in the art would not expect compounds of similar structure to have similar antipsychotic activity.

147. The prior art fails to suggest or render obvious the compound aripiprazole, a pharmaceutical composition containing aripiprazole, or a method of treating schizophrenia by administering a pharmaceutical composition containing aripiprazole, as recited in claims 12, 17, and 23 of the '528 patent.

148. Defendants will be unable to prove that any of the asserted claims 12, 17, or 23 of the '528 patent are invalid for obviousness.

2. Defendants' Obviousness-Type Double Patenting Defense Lacks Merit

149. Defendants assert that claims 12, 17, and 23 of the '528 patent are invalid for obviousness-type double patenting over claim 13 of the '416 patent directed to the unsubstituted butoxy compound. In making this argument, Defendants repeat the same unsupported factual assertions addressed above with regard to alleged obviousness of the claims under 35 U.S.C. § 103 in view of the same unsubstituted butoxy compound disclosed in the '416 patent. Otsuka therefore incorporates by reference its counter-facts set forth above rebutting Defendants' erroneous obviousness contentions based on the unsubstituted butoxy compound.

150. Because the '416 patent is prior art to the '528 patent, the issue of alleged obviousness-type double patenting is subsumed by the broader statutory inquiry of alleged obviousness under 35 U.S.C. § 103. There is no separate issue of obviousness-type double patenting in this case.

151. The asserted claims of the '528 patent are not invalid for obviousness-type double patenting. For all the reasons stated previously, claims 12, 17, and 23 of the '528 patent would not have been obvious in view of the entire disclosure of the '416 patent, including the disclosure of the unsubstituted butoxy compound. Therefore, *a fortiori*, those claims would not have been obvious in view of the unsubstituted butoxy compound of claim 13 of the '416 patent.

152. Claims 12, 17, and 23 of the '528 patent are patentably distinct from the separate invention defined by claim 13 of the '416 patent. Claims 12, 17, and 23 are directed to aripiprazole, a pharmaceutical composition containing aripiprazole for treating schizophrenia, and a method of treating schizophrenia by administering a pharmaceutical composition containing aripiprazole. Claim 13 of the '416 patent, on the other hand, is directed to a different chemical compound (the unsubstituted butoxy compound). The '416 patent describes the unsubstituted butoxy compound as an antihistamine, not an antipsychotic. Nothing in the prior art suggests selecting the unsubstituted butoxy compound as a lead compound for antipsychotic drug development, modifying it to obtain aripiprazole, or using aripiprazole to treat schizophrenia. Defendants' double patenting allegation is based on speculation and hindsight rather than the actual teachings of the prior art.

153. Defendants further argue that the asserted claims are invalid for obviousness-type double patenting in view of claim 30 of the '416 patent. This argument also is baseless. Because claims 12, 17, and 23 of the '528 patent would not have been obvious in view of the entire disclosure of the '416 patent for the reasons previously discussed, *a fortiori*, those claims would not have been obvious in view of any individual claim of the '416 patent, including claim 30.

154. Claims 12, 17, and 23 of the '528 patent, relating to aripiprazole and its use to treat schizophrenia, are patentably distinct from the separate invention defined by claim 30 of the

'416 patent. Claim 30 of the '416 patent is a broad "genus" claim covering literally billions of different carbostyryl derivatives. A person of ordinary skill in the art in 1988 could not possibly have identified aripiprazole from among those billions of compounds and would have had no clue that aripiprazole is a safe and effective antipsychotic.

155. Defendants' various arguments attempting to artificially narrow the scope of claim 30 from billions of compounds to one or two compounds (including aripiprazole) are once again based on hindsight. There is no factual basis in the prior art for any of Defendants' assertions with regard to how a person of ordinary skill allegedly would have arrived at aripiprazole from the broad scope of claim 30 of the '416 patent. Because the prior art fails to describe the chemical structure of aripiprazole or its therapeutic properties in treating schizophrenia, a person of ordinary skill could not have narrowed down the billions of compounds of claim 30 to aripiprazole or had any reasonable expectation of success in using aripiprazole to treat schizophrenia.

3. Defendants' Lack of Utility Defense Lacks Merit

156. Defendants also argue that claims 12, 17, and 23 of the '528 patent are invalid for lack of utility under 35 U.S.C. §§ 101/112 because the disclosure in the specification of the '528 patent allegedly is not adequate to support the use of aripiprazole as an antipsychotic. This argument is fatally flawed.

157. Claim 12 is directed to the compound aripiprazole. Claim 12 is not limited to any particular use of that compound and therefore Otsuka could satisfy the utility requirement of sections 101 and 112 by disclosing any practical utility for aripiprazole, including any pharmacological activity. Here, the specification of the '528 patent discloses that aripiprazole and the other compounds of the invention have the pharmacological activity of blocking

neurotransmission at dopamine receptors in the brain. That disclosure of anti-dopaminergic pharmacological activity satisfies the utility requirement with respect to claim 12.

158. Claim 17 of the '528 patent is directed to a pharmaceutical composition containing aripiprazole for treating schizophrenia, and claim 23 is directed to a method of treating schizophrenia by administering a pharmaceutical composition containing aripiprazole. The specific utility required by those claims—treatment of schizophrenia using aripiprazole—is repeatedly disclosed in the specification of the '528 patent.

159. A person of ordinary skill in the art in 1988 would have known how to use aripiprazole as an antipsychotic for the treatment of schizophrenia based on the disclosure of the '528 patent. No undue experimentation would have been required for a person of ordinary skill to use aripiprazole to treat schizophrenia as described in the '528 patent.

160. In addition, the specification of the '528 patent provides stereotypy test results in mice for aripiprazole, which persons skilled in the art would understand reasonably predict antipsychotic activity in humans suffering from the positive symptoms of schizophrenia.

161. Because Defendants performed no tests themselves, they have no basis to challenge the accuracy of the stereotypy test results presented in the specification. Aripiprazole is in fact highly potent in the stereotypy test as reported in the specification of the '528 patent and as further confirmed by extensive subsequent testing of the compound. Defendants cannot dispute that aripiprazole is highly potent in the stereotypy test.

162. Defendants assert that stereotypy test results are inadequate because the stereotypy test allegedly is predictive of EPS side effects rather than antipsychotic efficacy. This assertion is simply incorrect. The stereotypy test is a well-established screening test for assessing the dopamine blocking activity of compounds and has been widely and successfully

used for many years to predict antipsychotic activity. Otsuka incorporates by reference its additional rebuttal facts concerning the stereotypy test set forth in section C(8) below concerning the Hirose declaration.

163. Aripiprazole is indisputably useful to treat schizophrenia exactly as predicted by the stereotypy test. Indeed, it has been approved by the FDA as an antipsychotic drug (Abilify[®]) for the treatment of schizophrenia, and Defendants are seeking to market generic copies of Otsuka's Abilify[®] product specifically for the treatment of schizophrenia. Defendants cannot credibly maintain that aripiprazole is not useful to treat schizophrenia. The specification of the '528 patent correctly indicates that it is useful for that purpose based on its potency in the stereotypy test. No more is required to satisfy the utility requirement.

164. Defendants' infringement of the asserted claims of the '528 patent and copying of aripiprazole, and the commercial success of aripiprazole, further establish the utility of the claimed invention and preclude Defendants' arguments to the contrary.

165. For these reasons, Defendants will be unable to prove that the asserted claims are invalid for lack of utility under 35 U.S.C. § 101 or for failure to meet the "how to use" enablement requirement of 35 U.S.C. § 112.

C. THE '528 PATENT IS ENFORCEABLE

166. Defendants offer a confusing series of at least eight separate theories of inequitable conduct, yet fail to present sufficient facts to support any of their various theories. Specifically, Defendants fail to allege facts sufficient to establish by clear and convincing evidence that (1) information was misrepresented or withheld from the PTO; (2) the information allegedly misrepresented or withheld was material to patentability; (3) an individual substantively involved in the PTO proceedings regarding the '528 patent knew about the

information at the relevant times; (4) such individual knew that such information was material; and (5) such individual withheld or misrepresented the information with an intent to deceive the PTO.

167. Defendants' current assortment of inequitable conduct theories also is markedly different from those discussed in their expert reports. For example, Defendants now seek to premise their inequitable conduct theories in part on the alleged non-disclosure of particular references that were not addressed by Defendants' expert on PTO practice and procedure.

1. No Inequitable Conduct as to the Nakagawa Declaration

168. Defendants allege that Otsuka failed to disclose the Nakagawa declaration during the original prosecution and reexamination of the '528 patent. As discussed above, the Nakagawa declaration was submitted during the prosecution of another Otsuka patent directed to carbostyryl compounds, the '416 patent. Accordingly, this document is a PTO submission, not a printed publication, and therefore is not prior art. Indeed, no court has ever held that a declaration submitted to the PTO constitutes prior art, and this document would not have been considered prior art by anyone having knowledge of it.

169. The Nakagawa declaration also is not material to the prosecution of the '528 patent. The Nakagawa declaration presents test data from multiple tests, none of which is described as indicating efficacy for treating schizophrenia. Defendants focus on the mouse jumping test data presented in this declaration, but these data are different from the stereotypy test data disclosed in the '528 patent and submitted during the original prosecution and reexamination proceedings. Defendants fail to establish any relationship between the mouse jumping test data and the stereotypy test data and, in fact, there is no scientific correlation between results in one test with the other. Moreover, there is no evidence that the mouse jumping test has ever been used to develop a new antipsychotic drug.

170. Defendants' argument for the alleged materiality of the Nakagawa declaration relies on a misinterpretation of the data. For the reasons discussed previously, the Nakagawa declaration does not suggest the desirability of the unsubstituted butoxy compound as a lead compound in the development of a new antipsychotic drug, nor does it otherwise render the '528 patent claims obvious.

171. For purposes of their inequitable conduct arguments, Defendants contend that the mouse jumping test data in the Nakagawa declaration suggest the superiority of a butoxy linker group over a propoxy linker group in an improved antipsychotic drug. As noted above, however, one of ordinary skill in the art seeking to develop a new antipsychotic drug would have had little to no interest in mouse jumping test data. Even if one of ordinary skill in the art were interested in the mouse jumping data presented in the Nakagawa declaration for this purpose, these data would not suggest the use of a butoxy linker group. One of ordinary skill in the art would focus on the compounds that were the most potent in this test. The four most potent compounds presented in this declaration are propoxy-linked compounds, not butoxy-linked compounds. Indeed, eight of the nine compounds tested in the declaration are propoxy-linked compounds. Therefore, if anything, the Nakagawa declaration teaches a clear preference for propoxy-linked compounds, not butoxy-linked compounds.

172. Defendants also do not identify any individual substantively involved in the PTO proceedings regarding the '528 patent who in fact knew about the Nakagawa declaration or believed that it was prior art. There certainly is no evidence that anyone ever withheld it from the PTO with intent to deceive.

173. Defendants only name three individuals in their contested facts as possibly having knowledge of the Nakagawa declaration and allegedly having a duty to disclose this declaration:

Dr. Oshiro, Katuyoshi Yamamoto, and Arthur S. Garrett. Defendants point to no evidence that any of these individuals knew of the Nakagawa declaration during the relevant time period, knew of its alleged materiality, or withheld it from the PTO with deceptive intent. In fact, no such evidence exists.

174. Defendants further fail to establish that Mr. Yamamoto was substantively involved in any proceedings before the PTO regarding the '528 patent or that Mr. Garrett was involved in the reexamination proceedings concerning the '528 patent.

2. No Inequitable Conduct as to Otsuka's Characterization of the Unsubstituted Butoxy Compound

175. Defendants additionally argue that certain unnamed Otsuka representatives committed inequitable conduct during the reexamination proceedings because Otsuka argued that the references before the PTO during the reexamination did not contain any evidence that the unsubstituted butoxy compound may be useful in treating schizophrenia. Otsuka's argument concerning the unsubstituted butoxy compound was in fact correct with respect to the record during the reexamination and Defendants do not dispute this point. Instead, Defendants argue that Otsuka's arguments concerning the unsubstituted butoxy compound are contradicted by certain evidence that was not before the PTO, namely the Nakagawa declaration and attorney arguments presented during the prosecution of an entirely different patent, U.S. Patent No. 4,619,932 ("the '932 patent"). There is no such contradiction. In addition, even if there were a contradiction, Defendants point to no evidence that Otsuka's representatives responsible for making the arguments during the reexamination had any awareness of the Nakagawa declaration or the arguments from the '932 prosecution or had any duty to disclose this non-prior art evidence to the PTO.

3. No Inequitable Conduct as to the Parke-Davis "Work"

176. Defendants further allege that certain vaguely defined Parke-Davis "work" was withheld from the PTO. Defendants, however, do not identify any prior art documents relating to this Parke-Davis work that were intentionally withheld from the PTO.

177. Defendants first cite to an internal Otsuka memorandum authored by S. Haruki and addressed to Manager Kabe. This is a non-public document and therefore does not constitute prior art. Moreover, Defendants' translation of this memorandum is inaccurate and misrepresents the contents of this memorandum. The Haruki memorandum also is not material to the prosecution of the '528 patent in that it discusses work on coumarin compounds that are structurally distinct from the carbostyryl compounds disclosed and claimed in the '528 patent.

178. Defendants next cite to a "1987 Wise Poster" document that they allege was presented during a scientific meeting in 1987. Defendants have presented no evidence, however, that this specific document was ever made available to the public so as to constitute a prior art printed publication, and will be unable to do so at trial.

179. Even if it were prior art, the Wise poster would not have been material to the prosecution of the '528 patent. As with the Haruki memorandum, the Wise poster is directed to coumarins, which are structurally distinct from carbostyryls. Moreover, even if Wise's work on coumarins had any relevance to carbostyryl compounds, the Wise poster does not suggest the use of a butoxy linker in either coumarins or carbostyryls, as Defendants contend. The Wise poster in fact identifies a propoxy-linked compound, PD-116795, as the key and most promising antipsychotic compound, thus teaching a preference for that linking group. The Wise poster also notes that the tested coumarin compounds lost all activity upon substitution of the phenyl ring, thus further teaching away from the structural features of aripiprazole, which has a disubstituted phenyl ring.

180. The pharmacological tests described in the Wise poster also bear no relation to the stereotypy test used by Otsuka to discover aripiprazole.

181. Another Parke-Davis document, the '456 patent, concerns a broad genus of coumarin compounds and would not have been material to the prosecution of the '528 patent. The '456 patent teaches a clear preference for coumarin compounds with propoxy linkers, and teaches away from aripiprazole. For example, pharmacological test data are provided for only two coumarin compounds with a phenyl piperazine group, both of which are propoxy-linked and are unsubstituted at the phenyl group. Moreover, the pharmacological tests described in the '456 patent bear no relation to the stereotypy test used by Otsuka to discover aripiprazole.

182. As with the Nakagawa declaration, Defendants do not identify any individual who had a duty to disclose the Parke-Davis work, knew about the Parke-Davis work, believed it to be material, and withheld this information from the PTO with an intent to deceive.

183. Defendants only name a single individual, Dr. Oshiro, in their allegations concerning the Parke-Davis work. Defendants allege Dr. Oshiro may have had knowledge of this work because he was copied on the memorandum from S. Haruki to Manager Kabe. Defendants do not identify any evidence, however, that Dr. Oshiro ever received this memorandum or became aware of its contents. This document was not located in or produced from Dr. Oshiro's files and Dr. Oshiro does not recall ever having seen this document. Defendants do not even suggest that Dr. Oshiro was aware of the Wise poster, and he was not.

184. Moreover, even assuming that Dr. Oshiro knew about the Parke-Davis work during the relevant period, which he did not, Defendants fail to establish that Dr. Oshiro believed any of this work was material to the patentability of the claimed compounds or that he withheld it from the PTO with deceptive intent.

4. No Misrepresentation of Prior Art in the Specification

185. Defendants suggest that certain Otsuka employees, namely Dr. Oshiro and Dr. Minamikawa, somehow sought to mislead the PTO through their disclosure of relevant patents in the “Background of the Invention” section of the ’528 patent specification. This section of the patent specification provides a comprehensive discussion of “carbostyryl derivatives known in [the] prior art,” and reads as follows:

Among carbostyryl derivatives known in prior art, those disclosed in U.S. Patent No. 4,734,416; Canadian Patent No. 1,117,110; British Patent No. 2,017,701; German Patent Nos. 2,911,108, 1,912,105 and 2,953,723; Japanese Patent Kokai (Laid-open) Nos. 54-130,587 (1979), 55-127,371, (1980) and 62-149,664 (1987) are having chemical structural formulas of upper conception of carbostyryl derivatives of the present invention.

Furthermore, carbostyryl derivatives disclosed in U.S. Pat. No. 4,234,585 and European Patent No. 226,441 have chemical structural formula similar to that of carbostyryl derivatives of the present invention, but the pharmacological activities thereof are different from those of possessed by the carbostyryl derivatives of the present invention.

In addition to the above, the carbostyryl derivatives disclosed in U.S. Pat. No. 4,234,584 have chemical structural formula similar to that of carbostyryl derivatives of the present invention and also have pharmacological activities similar to those of shown by carbostyryl derivatives of the present invention.

Carbostyryl derivatives disclosed in Australian Patent No. 50252/85, Japanese Patent Kokai (Laid-open) Nos. 58-43952 (1983), 56-49359 (1981), 56-49360 (1981) and 56-49361 (1981) have substituents different from those of the carbostyryl derivatives of the present invention.

186. As recited above, the first patent disclosed in this listing of “carbostyryl derivatives known in [the] prior art” is the ’416 patent, which Defendants rely upon in their obviousness defense. The ’416 patent discloses and claims a broad genus of carbostyryl derivatives and about 500 specific carbostyryl derivatives. The ’416 patent does not specifically

disclose or claim any of the specific compounds claimed in the '528 patent, including aripiprazole.

187. In addition to the '416 patent, the first paragraph in the listing of "carbostyryl derivatives known in [the] prior art" identified other patents related to the '416 patent and having similar disclosures. These patents include German Patent No. 2,912,105 ("the DE '105 patent"), Canadian Patent No. 1,117,110, and British Patent No. 2,017,701. A typographical error in the number of the German patent was corrected during reexamination ("1,912,105" was corrected to "2,912,105"). There is no evidence that the incorrect number was anything other than a typo. Like the '416 patent, each of these foreign patents discloses the same broad genus of carbostyryl derivatives and numerous specific examples of carbostyryl derivatives. None of these patents discloses or claims the specific compounds claimed in the '528 patent, including aripiprazole.

188. The prior art disclosure to the PTO in the patent specification reflects Otsuka's good faith in prosecuting the application leading to the '528 patent. The paragraphs of prior art discussed in the patent specification identify highly relevant references disclosing a broad genus of carbostyryl compounds and many specific carbostyryl derivatives. Indeed, these references disclose the unsubstituted butoxy and OPC-4392, the compounds that the Defendants have contended are the closest prior art compounds.

189. The specification does not indicate, as Defendants contend, that the first paragraph of the prior art discussion describes the references listed therein as being the least relevant. Defendants cannot identify any language in support of this illogical contention and there is certainly no such language in the first paragraph. The very first words of this paragraph are "[a]mong carbostyryl derivatives known in the prior art," which directly indicates the relevance of these references to the '719 application, titled "Carbostyryl Derivatives." Moreover,

the fact that these reference are included in the *first* paragraph in the discussion of “carbostyryl derivatives known in the prior art” strongly suggests that these references may be the *most* relevant.

190. The Examiner who examined the '719 application, Examiner Turnipseed, was not led away from these references. During the prosecution of the '528 patent, the Examiner cited to the '840 patent, which is a division of the '416 patent, the patent listed first in the references disclosed in the “Background of the Invention.” Because it is a division of the '416 patent, the '840 patent shares the same disclosure (including all the same carbostyryl derivatives) as the '416 patent and only differs with respect to the patent claims.

**5. No Withholding of the '416 Patent or Its Foreign Counterparts
During the Prosecution of the '528 Patent**

191. Defendants suggest, with no evidentiary basis, that Dr. Oshiro withheld from the PTO the '416 patent and its foreign counterparts, including DE '105, Swedish Application No. 434,945, Austrian Patent AT 376432 and Finnish Patent FI0704. As discussed above, the '416 and DE '105 patents were each disclosed to the PTO in the “Background of the Invention” section of the patent specification, although the description of DE '105 included an obvious typo. Under these circumstances, there can be no argument that Dr. Oshiro, or any other individual, intentionally withheld these references from the PTO. The remaining foreign counterpart patents are all cumulative to the '416 and DE '105 patents because they disclose the same compounds. There is no basis for any contention that Dr. Oshiro withheld these references from the PTO.

192. The PTO specifically considered the '416 and DE '105 patents during the reexamination proceedings and concluded that they were cumulative to the '840 patent, which had been considered by the PTO during the original prosecution. Accordingly, for this reason as

well there is no basis for any contention that Dr. Oshiro withheld from the PTO the '416 patent or its foreign counterparts.

6. No Withholding of the Banno Article or References Cited Therein

193. Defendants further contend Dr. Oshiro should have submitted to the PTO a November 1988 article relating to carbostyryl derivatives authored by Kazuo Banno and others ("the Banno article") and certain references cited in the Banno article. Defendants presented these baseless arguments for the first time in their Pretrial Order submissions. Indeed, Defendants' own patent expert has not contended that any of these references should have been provided to the PTO.

194. The Banno article post-dates the October 1988 priority date of the '528 patent and therefore is not prior art. Accordingly, Defendants cannot argue that this document should have been submitted to the PTO or that Dr. Oshiro withheld it with an intent to deceive. The Banno article also is cumulative to documents considered by the PTO during the original prosecution proceedings and the reexamination, including the '840 patent.

195. Even though the Banno article is not prior art, Otsuka submitted it to the PTO for consideration during reexamination of the '528 patent. The PTO confirmed that the '528 patent claims are patentable over the Banno article. There is no evidence of any withholding of the Banno article from the PTO.

196. As to the references cited in the Banno article, these references are either cumulative to information that was already before the PTO or completely irrelevant to the prosecution of the '528 patent. The first references identified by Defendants are two articles concerning OPC-4392. As previously explained, a person of ordinary skill in October 1988 would have concluded that OPC-4392 was not a promising drug candidate because it did not adequately treat the positive symptoms of schizophrenia and had potentially serious neurological

side effects. The two publications cited by Defendants concern pre-clinical testing of OPC-4392 in rodents. Because unsuccessful clinical results in humans for OPC-4392 were available by 1988, pre-clinical results in rodents would have been of little interest to persons skilled in the art. Further, as shown by aripiprazole's ability to treat the positive symptoms of schizophrenia and OPC-4392's failure to do so, aripiprazole and OPC-4392 do not share similar pharmacological properties. OPC-4392 was therefore not relevant to the compounds of the '528 patent.

197. Further, OPC-4392 was disclosed in European Patent No. 226,441 ("EP '441"), which was identified in the specification of the '528 patent. The PTO confirmed the patentability of the claims over EP '441 and several other publications relating to OPC-4392 during the reexamination of the '528 patent, rendering the publications cited by Defendants cumulative. There is no evidence that anyone involved in the prosecution or reexamination of the '528 patent ever deliberately withheld any publications or information concerning OPC-4392 from the PTO with deceptive intent.

198. The remaining references identified by Defendants are articles directed to carbostyryl compounds developed for use in treating conditions other than schizophrenia. The compounds described in these articles are structurally distinct from the carbostyryl compounds disclosed and claimed in the '528 patent and these compounds are also described as having pharmacologically distinct applications as beta-blockers or blood platelet inhibitors. Defendants' argument that these articles are relevant to the '528 patent is specious.

199. Defendants also have no basis to argue that Dr. Oshiro believed these documents to be material or that he withheld them from the PTO with an intent to deceive.

7. Dr. Oshiro Did Not Engage in Any Inequitable Conduct in Connection with His Declaration

200. During the prosecution of the '528 patent, Dr. Oshiro submitted a declaration establishing the superiority of the claimed compounds over prior art compounds identified by the Examiner. Defendants raise a number of baseless allegations in connection with Dr. Oshiro's declaration.

201. Defendants contend that Dr. Oshiro withheld "his prior art patents and a published application that disclosed additional homologues and the OPC-4392 publications." Defendants fail to identify with any specificity these prior art patents, published application, and OPC-4392 publications. From this vague description, however, it appears that the Defendants are referencing materials that would be cumulative to the multiple carbostyryl references disclosed to the PTO in the '528 patent specification and/or considered by the PTO during the prosecution of the '528 patent. These arguments fail for all the reasons discussed above.

202. Defendants also appear to contend that Dr. Oshiro possessed pharmacological data for Example 317 of the DE '105 patent, which Dr. Oshiro allegedly should have disclosed to the PTO. Defendants do not identify any evidence that Dr. Oshiro indeed possessed pharmacological data for Example 317 during the original prosecution of the '719 application, or that Dr. Oshiro intentionally withheld such data with intent to deceive the PTO.

203. The anti-epinephrine activity data for Example 317 Defendants identify do not contradict in any way the conclusions presented in Dr. Oshiro's declaration. To the contrary, the data associated with the compound of Example 317, including both anti-epinephrine and anti-apomorphine test results, fully support the patentability of the compounds claimed in the '528 patent. In fact, data for this same compound were presented to the PTO during the

reexamination proceedings and the PTO concluded that the data demonstrated “clear unexpected results” establishing the patentability of the claimed compounds over the prior art.

204. Defendants appear to contend that the Oshiro declaration misrepresented the procedures used in testing the prior art compounds identified by the Examiner. Defendants do not identify any contemporaneous evidence, however, that would indicate that the testing was not done, or that it was misrepresented by Dr. Oshiro. Defendants’ sole support for this assertion is deposition testimony given almost twenty years after the alleged fact. That Dr. Oshiro did not personally perform the testing and does not recall the specific details of who performed these tests does not establish any inaccuracies or misrepresentations in Dr. Oshiro’s declaration. Dr. Oshiro explained the active role he played in this type of testing but candidly admitted that, 20 years after the fact, he does not remember today the precise details of how this testing was carried out. Defendants decided to conduct no testing of their own and have no basis to dispute Otsuka’s test data.

205. Defendants also appear to contend that the Oshiro declaration is false and misleading because the stereotypy test allegedly does not establish that the claimed compounds can be used for treating schizophrenia. Defendants cannot establish that Dr. Oshiro incorrectly relied on the stereotypy test in his declaration. Dr. Oshiro used this test as the first screening test in the research that resulted in his discovery of aripiprazole. Otsuka incorporates by reference its additional rebuttal facts concerning the stereotypy test set forth in section C(8) below concerning the Hirose declaration.

8. Dr. Hirose Did Not Engage in Any Inequitable Conduct in Connection with His Declaration

206. During the reexamination of the ’528 patent, Dr. Tsuyoshi Hirose submitted a declaration establishing the superiority of the claimed compounds over specific prior art

compounds that Otsuka and the PTO agreed were the closest prior art. As with the Oshiro declaration, Defendants raise a number of baseless allegations in connection with Dr. Hirose's declaration.

207. In his declaration, Dr. Hirose presented test data concerning compounds that he identified as representative of those claimed in the '528 patent as compared to other compounds that he identified as the closest prior art compounds. Defendants dispute the accuracy of Dr. Hirose's statements identifying these compounds as representative compounds and closest prior art compounds and suggest that these alleged inaccuracies support their inequitable conduct claims. Defendants do not explain, however, in what way Dr. Hirose's statements were not true, nor do they explain what prior art compounds were closer than those tested in the Hirose declaration.

208. The compounds tested in the Hirose declaration were chosen by agreement between Otsuka and the PTO. For this reason alone, Dr. Hirose had ample reason to offer his opinions concerning the selection of these compounds and did not commit inequitable conduct in doing so. Moreover, prior to signing his declaration, Dr. Hirose consulted with various groups at Otsuka, including but not limited to the synthesis group, the statistics group, and the intellectual property department, to ascertain that his opinions were correct. Defendants fail to point to any evidence that Dr. Hirose submitted those opinions with an intent to deceive the PTO.

209. Defendants suggest that Dr. Hirose acted improperly by allowing attorneys to assist in the drafting of his declaration. There is nothing improper in having attorneys assist with drafting a declaration and this is in fact routine with respect to documents submitted in prosecution before the PTO.

210. Defendants assert that “Dr. Oshiro, an organic chemist, testified that the unsubstituted butoxy compound could be recognized as structurally closer than the homologues identified by Dr. Hirose in the Hirose declaration.” Defendants misrepresent Dr. Oshiro’s testimony. Dr. Oshiro testified that he personally believed that the dichloro-substituted compound tested by Dr. Hirose in his declaration was structurally closer than the unsubstituted butoxy compound that was not tested. Dr. Oshiro simply acknowledged that others might conclude otherwise. Regardless of Dr. Oshiro’s actual testimony, however, Defendants fail to establish how Dr. Oshiro’s statement offered years after Dr. Hirose signed his declaration diminishes the good faith and due diligence with which Dr. Hirose presented his opinions in that declaration.

211. Defendants assert Dr. Hirose misled the PTO in his declaration by identifying activity in the stereotypy test as a strong indicator of a compound’s antipsychotic potency. According to Defendants, this statement was misleading because the stereotypy test allegedly is indicative of EPS side effects rather than antipsychotic activity. Defendants are simply wrong on this point. As reflected in the literature, the stereotypy test is well-correlated with antipsychotic activity in humans. *See* the representative publications and patents at PTX 413-461, 467, 470-471, 477 and 488-532.

212. Dr. John Marshall, a pharmacologist retained by Apotex, acknowledged that activity in the stereotypy test is “well-correlated with anti-schizophrenic activity in humans.” Similarly, Apotex’s chemistry expert Dr. Neal Castagnoli admitted that the stereotypy test is an “assay used to evaluate the potential of a compound to treat schizophrenia.” Thus, two of Defendants’ own technical experts would not support Defendants’ litigation-driven assertion that the stereotypy test is not a valid screen for potential antipsychotic activity.

213. Defendants' position concerning the stereotypy test cannot be reconciled with the fact that aripiprazole does not cause significant EPS. As demonstrated in the Hirose declaration, aripiprazole is quite potent in the stereotypy test. Thus, according to Defendants' hypothesis, one would expect aripiprazole to cause substantial EPS in humans. Aripiprazole, however, has an extremely low propensity to cause EPS. Defendants have no explanation for aripiprazole's lack of EPS.

214. Otsuka's reasonable reliance on the stereotypy test also is confirmed by the fact that aripiprazole is an effective antipsychotic exactly as predicted by the test. The test indisputably worked as a screen for antipsychotic activity and allowed Otsuka to identify aripiprazole as a potential antipsychotic. If Otsuka had followed Defendants' hypothesis that the stereotypy test only shows potential EPS, it never would have discovered this important new drug. Defendants do not even attempt to reconcile aripiprazole's clinical efficacy and lack of EPS with their interpretation of the stereotypy test results as allegedly only indicating a high potential for EPS.

215. Otsuka's reasonable reliance on the stereotypy test also is supported by the activity of other antipsychotics in this test. Every clinically effective antipsychotic inhibits apomorphine-induced stereotypy at least to some extent. This appears to be true both for typical and atypical antipsychotic drugs, despite the fact that atypical antipsychotics generally do not cause EPS. Because both typical and atypical antipsychotics inhibit stereotypy, it is reasonable to expect that a compound that inhibits stereotypy potentially will have antipsychotic properties irrespective of whether it may also cause EPS. Defendants have no credible evidence to the contrary.

216. The stereotypy test has been widely used by many research groups as an indicator of potential antipsychotic activity. Major pharmaceutical companies have used the stereotypy test to screen for potential antipsychotic compounds. This has been true beginning well before and continuing well after the 1988 priority date at issue in this case. There are dozens of scientific publications and patents describing the stereotypy test as a screen for potential antipsychotic activity, illustrating the widespread use of the test for that purpose.

217. The stereotypy test is the only antipsychotic assay identified in patents that describe four of the six atypical antipsychotics approved in the United States since 1975. These four antipsychotics are all considered to be “atypical” for their low propensity to cause EPS, further refuting Defendants’ “EPS” hypothesis. Accordingly, given the successful use by Otsuka and others of the stereotypy test in antipsychotic drug development, it was entirely reasonable for Otsuka to rely on that test as a measure of potential antipsychotic potency.

218. A person of ordinary skill in the art in 1988 would have interpreted the potency of the ’528 patent compounds in the stereotypy test as indicating that the compounds are dopamine receptor antagonists having potential antipsychotic activity.

219. Defendants fail to identify clear and convincing evidence that the stereotypy test is in fact indicative of EPS or that Dr. Hirose believed that to be the case.

220. Defendants fail to establish that Dr. Hirose’s opinion in his declaration concerning the stereotypy test was in any way inaccurate or misleading.

221. Defendants also do not identify any evidence that Dr. Hirose offered his opinion concerning the stereotypy test with an intent to mislead the PTO.

222. Defendants further assert that the Hirose declaration is false and misleading because the data therein are allegedly “confounded and biased and cannot be meaningfully

compared due to failure to properly blind the study and standardize scoring by different observers.” Defendants do not identify any facts in support of this speculative argument. Otsuka will present at trial a statistical analysis of these data, conducted by Otsuka’s expert statistician, Dr. Thisted. Dr. Thisted’s analysis yields no evidence of any confounding or bias in the data. Defendants chose to not conduct any statistical analysis of their own and will be unable to rebut Dr. Thisted’s analysis.

223. Defendants further raise vague criticisms concerning the testing protocols used to generate the data underlying the Hirose declaration. These protocols were standard, completely proper, and accurately described how the testing was conducted. Moreover, having conducted no testing of their own, Defendants have no basis to criticize Otsuka’s testing procedures.

224. Defendants contend Dr. Hirose misled the PTO in stating that anti-epinephrine activity is a significant indication for showing side effects. Defendants fail to establish that this anti-epinephrine activity statement is false or misleading. Defendants do not dispute that a compound with significant anti-epinephrine activity is likely to cause orthostatic hypotension, and that orthostatic hypotension is a serious side effect.

225. Defendants appear to suggest that Dr. Hirose misled the PTO in explaining that the data presented in his declaration demonstrated the unpredictable superiority of the claimed compounds as compared to the prior art compounds. Defendants cannot show that Dr. Hirose’s conclusion is false or misleading in any way.

226. The PTO considered the data in the Hirose declaration and agreed with Dr. Hirose’s conclusion. In reporting its “Reexamination Reasons for Patentability/Confirmation,” the PTO explained that it found claims 1-21 allowable “since applicants have compared their compounds with the closest prior art. The ones with just one difference in the linker chain,

propyloxy to a butoxy cha[in], show[] a clear unexpected result in the ED50 values.” The “Reexamination Reasons for Patentability/Confirmation” was signed by Primary Examiner Rita J. Desai, Supervisory Patent Examiner Cecilia J. Tsang, and Special Program Examiner William R. Dixon, Jr. The conclusion regarding patentability of the ’528 patent subject matter was thus a consensus decision by at least three capable, senior-level Patent Examiners.

227. In sum, Defendants will be unable to prove that Dr. Hirose, Dr. Oshiro, or anyone else associated with the prosecution or reexamination of the ’528 patent knowingly withheld any material information from the PTO, or made any material misrepresentation to the PTO, with deceptive intent. None of Defendants’ theories of inequitable conduct will succeed.

9. Defendants’ Remaining Assertions Provide No Support for Their Inequitable Conduct Theories

228. In addition to the specific arguments addressed above, Defendants also provide several factual assertions that may relate to their inequitable conduct theories. These assertions, however, do not overcome the multiple deficiencies in Defendants’ arguments explained above.

229. Defendants allege that numerous “materials” were not cited to or considered by the PTO during the original prosecution proceedings or reexamination. These materials are either non-prior art, cumulative to materials cited to or considered by the PTO, or simply irrelevant to the prosecution and reexamination of the ’528 patent. Defendants’ vague allegations concerning these materials provide no support for their inequitable conduct theories.

230. Defendants further point to numerous “statements” to the PTO. These statements are either paraphrased incorrectly, cited out of context, simply irrelevant, or otherwise provide no support for Defendants’ inequitable conduct theories.

231. Defendants further paraphrase numerous provisions from the Manual of Patent Examining Procedure (“MPEP”). As with Defendants’ “statements” to the PTO, Defendants’

MPEP citations are either paraphrased incorrectly, cited out of context, irrelevant, or otherwise provide no support for Defendants' inequitable conduct theories.

(2) Plaintiff intends to prove the following contested facts with regard to damages: (This must include each item of damages, the amount of each item, the factual basis for each item and, if punitive damages are claimed, the facts upon which plaintiff will rely to establish punitive damages).

1. Otsuka is not seeking damages for the claims currently set for trial in this matter. Otsuka, however, reserves the right to seek damages should Defendants engage in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of Defendants' generic aripiprazole products described in Defendants' respective ANDAs before the expiration of the '528 patent. Otsuka further reserves the right to seek its costs and attorney fees associated with its exceptional case claim pursuant to 35 U.S.C. §§ 285 and 271(e)(4).

2. With respect to Otsuka's request for entry of a permanent injunction, the evidence establishes that (1) Otsuka will suffer irreparable injury in the absence of an injunction; (2) remedies available at law are inadequate to compensate Otsuka for that injury; (3) considering the balance of hardships between Otsuka and Defendants, a remedy in equity is warranted; and (4) the public interest would not be disserved by entry of a permanent injunction precluding infringement of the '528 patent.

3. In the absence of a permanent injunction, Otsuka would suffer significant noncompensable injury in the form of: (1) irreversible price erosion and lost market share; (2) reduction or elimination of ongoing clinical research aimed at identifying and developing new medical uses for aripiprazole; (3) loss of goodwill of patients and physicians; and (4) potential layoffs of sales personnel and other skilled Otsuka employees.

5. DEFENDANTS' CONTESTED FACTS (State separately for each defendant. See instructions above).⁴

(1) Defendants intend to prove the following contested facts with regard to liability.

Defendants reserve the right to revise their contested facts in light of the Court's decisions and other rulings. *Any such application to revise would be subject to a showing of manifest injustice.*

A. Background

1. Anti-Schizophrenic Drug Development Prior to 1988⁵

1. Schizophrenia is a central nervous system disorder characterized by what are known as "positive" and "negative" symptoms. Positive symptoms include hallucinations and delusions, while negative symptoms include flat affect, poverty of speech, inability to experience pleasure, lack of desire to form relationships, and lack of motivation.

2. The first class of drugs developed for the treatment of schizophrenia were known as "typical" antischizophrenic (also known as antipsychotic) drugs. These drugs, including chlorpromazine and haloperidol, were effective at treating the positive symptoms of schizophrenia, but not the negative symptoms.

3. In the 1960's, researchers discovered that the typical antischizophrenic drug chlorpromazine worked by reducing dopamine activity in the brain. Dopamine is a neurotransmitter, which is a substance that transmits nerve impulses across synapses. Chlorpromazine, it was found, reduced dopamine activity by blocking dopamine receptors in the brain.

⁴ Defendants object to Plaintiff's inclusion of facts, arguments and contemplated testimony by experts that was not included in Plaintiff's expert reports. Defendants also object to Plaintiff's reliance on the findings in the *Janssen* case.

⁵ The several headings are merely intended to improve readability. Facts mentioned under one heading are typically relevant to subject matter discussed under other headings even though those facts are not also recited under those headings.

4. Based on the discovery of chlorpromazine's mechanism of action, researchers began working under the assumption that an antischizophrenic drug needed to inhibit dopamine transmission in the brain in order to be effective. Accordingly, researchers based the pharmacological tests they used to identify potential candidate antischizophrenic drugs on the then-burgeoning dopamine hypothesis—*i.e.*, that an increased level of dopamine causes symptoms of schizophrenia.

5. Researchers engaged in discovering potential antischizophrenic drugs at that time typically performed tests on rodents to investigate the ability of candidate compounds to antagonize (or inhibit) the effects of substances such as amphetamine or apomorphine that were known to increase dopamine levels (known as “pro-dopaminergic agents”). Apomorphine, for example, was observed to induce in rodents a series of behaviors, such as increased locomotor activity (walking or moving from one location to another), climbing, and at higher doses, stereotyped behavior, which is defined as the continuous repetition of behavioral acts that have no apparent function. In rodents, stereotypy can manifest itself as repetitive sniffing, head bobbing, licking, or gnawing. Typical antischizophrenic drugs are relatively potent in stereotypy tests. Spontaneous locomotion had been found to be a superior test for finding potential antipsychotic activity, being the only test to correctly identify 40 out of 40 antipsychotics as such.

6. Typical antischizophrenic drugs were also known to induce in animals a condition called catalepsy, which is a state of diminished responsiveness associated with waxy rigidity of the muscles. If an animal has catalepsy, it will tend to remain in a posture set by an experimenter. Thus, the catalepsy test was also used as a screening assay for potential typical antischizophrenic drugs. Like the stereotypy test, activity in the catalepsy test is indicative of a

compound's ability to block dopamine transmission. Therefore, compounds that had activity in the catalepsy test were thought, at the time, to have the potential to treat schizophrenia.

7. Although typical antischizophrenic drugs are effective in treating the positive symptoms of schizophrenia, they can cause severe side effects. One side effect of typical antischizophrenics is the propensity to cause extrapyramidal symptoms ("EPS"), which include involuntary, irregular muscle movements, restlessness (akathisia), and the inability to initiate movement. Another side effect is prolactin elevation (hyperprolactinemia), which can lead to breast enlargement in men, milk production in women, and bone wasting. An additional side effect is a sudden decrease in blood pressure (orthostatic hypotension), which may cause the patient to pass out when standing up. Despite these various drawbacks, typical antischizophrenic drugs are still used today as one of the several options for treating schizophrenia.

8. Two breakthroughs in the 1970s refocused the approach to antipsychotic drug discovery. The first of these breakthroughs was the discovery of clozapine. Clozapine treated the positive and negative symptoms of schizophrenia without causing EPS or prolactin elevation, and became the first "atypical" antischizophrenic drug.

9. Unlike chlorpromazine and haloperidol, clozapine did not strongly antagonize apomorphine-induced stereotypy. The discovery of clozapine therefore taught those in the field that an antipsychotic that weakly antagonized stereotypy could effectively treat the symptoms of schizophrenia without producing EPS side effects.

10. Unfortunately, it was discovered that clozapine can cause a fatal decrease in white blood cells called agranulocytosis. Clozapine is still used today, but with careful monitoring of patients and frequent blood testing.

11. The second breakthrough was the discovery that antagonism of dopamine receptors in some parts of the brain was correlated with antipsychotic activity, whereas antagonism of dopamine receptors in other parts of the brain was correlated with unwanted EPS (the "dissociation hypothesis"). The region of the brain known as the striatum (part of the nigrostriatal system), which is directly involved in motor control, became correlated with unwanted EPS. The region of the brain known as the nucleus accumbens (part of the mesolimbic system or limbic region), which is involved with locomotion, became correlated with antipsychotic activity.

12. Because of these breakthroughs, researchers began to reconsider the tests they used to screen for potential antipsychotics. Tests that were indicative of dopamine antagonism in the limbic region (part of the mesolimbic and mesocortical dopamine pathways), such as the apomorphine-induced locomotion test, were correlated with measuring antipsychotic activity. In contrast, tests that were indicative of dopamine antagonism in the striatum (part of the nigrostriatal dopamine pathway), such as the apomorphine-induced stereotypy test, were correlated with measuring unwanted EPS. Similarly, tests indicative of antipsychotic activity in which clozapine had only weak or moderate effects were also reconsidered. Researchers therefore began to look for compounds that only weakly inhibited stereotypy.

13. In addition, the catalepsy test was abandoned as a test for potential antischizophrenic activity because activity in the catalepsy test became indicative of dopamine antagonism in the striatum and thus a compound's ability to cause unwanted EPS.

14. The dissociation hypothesis was one of the leading hypotheses driving antischizophrenic drug development in the 1980s and later. It became more accepted by

researchers in the field than other hypotheses, such as the “anti-cholinergic hypothesis” and the serotonergic hypothesis.

15. While one of ordinary skill in the art would have been aware of these hypotheses, her consideration of lead compounds would not be limited by them.

16. As of 1988, it was therefore the desire of those working in the field of antischizophrenic drug development to find a drug that would treat both the positive and negative symptoms of schizophrenia; not cause EPS or agranulocytosis; and would otherwise have a good side effect profile.

17. Over the last half century, the vast majority of drug research in the antipsychotic field has been performed in the research labs of large private corporations and smaller biotechnology companies. This research is directed at molecules that can be made into a commercial product. As such, a strong motivating factor, and one which is rarely acknowledged to the public, is to find a proprietary compound that can be patented and for which no one else has rights.

18. As a practical matter, avoiding the patents of others (or taking a license under them) as well as obtaining protective patents to the desired molecule and structurally similar or related compounds such as homologs, isomers, and analogs (which will usually have similar properties) are important considerations to medicinal chemists. In the real world, medicinal chemists may consider many compounds in the literature and their modifications useful for certain therapeutic purposes, but will not pursue them commercially if they are covered by the patents of others.

2. Drug Discovery

19. Medicinal chemists routinely make changes to chemical compounds in order to study the effects of structural change on biological activity. Through these routine, systematic

modifications, medicinal chemists develop what are known as structure-activity relationships (SARs), which correlate the effects of the chemical substituents on a molecule with their biological activity.

20. An SAR typically includes the systematic placement of different substituents, which are atoms or groups of atoms, onto a starting compound's molecular scaffold or "core" structure.

21. Chlorine is one of the most common substituents used in SAR studies of central nervous system ("CNS") drugs (which encompasses the field of antipsychotic drugs), and is often the first substitution to be considered. Among other things, chlorine substituents appear to enhance lipophilicity which is a compound's ability to dissolve in fats, oils, lipids, and non-polar solvents, and thus enhance a molecule's ability to penetrate the "blood-brain barrier" that protects the brain from the action of drugs and chemicals. In fact, several successful CNS agents, such as chlorpromazine, haloperidol and clozapine, have chlorine substituents. Chlorine is therefore one of the most predictable substitutions used in CNS drug development.

B. Overview of Otsuka's Development and Patenting of Carbostyryl Derivatives

22. Since the 1970s, Otsuka has been actively engaged in the development of carbostyryl derivatives as central nervous system drugs. Otsuka has filed numerous patents and patent applications, and published several articles, detailing the types of activity of these carbostyryl derivatives.

23. On March 30, 1978, Otsuka filed the first application in the chain that eventually issued as U.S. Patent No. 4,734,416 (the "'416 patent"). Otsuka subsequently filed foreign counterparts to this application. The '416 patent issued almost 10 years later on March 29, 1988.

24. The '416 patent discloses, among other compounds, 7-isomer carbostyryl derivatives, including ones with a propoxy (three carbon) linker and one with a butoxy (four carbon) linker.

25. On October 31, 1988, a few months after the '416 patent issued, Otsuka filed Japanese patent application JP 63-276953 directed to the 7-isomer series of the carbostyryl compounds disclosed in the '416 patent family.

26. On October 20, 1989, Otsuka filed U.S. patent application 07/424,719 (the "'719 application"), which eventually issued as the '528 patent. The '719 application claims priority to Otsuka's October 31, 1988 Japanese application.

C. The '416 and '528 Patents Both Cover Otsuka's Abilify Product

27. In 2003, Otsuka listed aripiprazole as a new chemical entity in the FDA publication entitled Approved Drug Products with Therapeutic Evaluations, commonly known as the "Orange Book." The Orange Book identifies drug products approved on the basis of safety and effectiveness by the FDA under the Federal Food, Drug, and Cosmetic Act.

28. There are two requirements for listing a patent in the Orange Book: (1) the patent must claim the drug or a method of using the drug that is the subject of an NDA; and (2) a claim of patent infringement could reasonably be asserted by the NDA holder or patent owner for the unauthorized manufacture, use, or sale of the drug that is the subject of the NDA.

29. In the 2004 edition of the Orange Book, Otsuka listed both the '416 patent and the '528 patent as patents covering the active ingredient in Abilify, aripiprazole. Otsuka therefore acknowledged that the '416 patent claimed aripiprazole or a method of using aripiprazole as a schizophrenic agent and that a claim for patent infringement of the '416 patent could reasonably be asserted for the unauthorized manufacture, use, or sale of aripiprazole.

30. The '416 patent expired in March 2005. The 2006 edition of the Orange Book was the first edition to list only the '528 patent as covering aripiprazole.

31. Without the '528 patent, Otsuka would have had no protection for aripiprazole in the United States as of March 2005, when the '416 patent expired.

D. The '528 Patent

1. Asserted Claims 12, 17, and 23

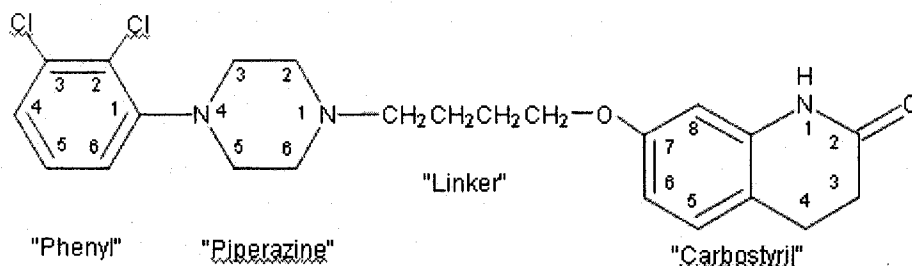
32. There are three patent claims at issue in this case, claims 12, 17, and 23 of the '528 patent.

33. Claim 12 reads:

12. 7-{4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydrocarbostyryl.

This is the chemical name for the compound aripiprazole.

34. Aripiprazole has the following structural formula:



35. Because there is no double bond between the third and fourth carbon atoms in the carbostyryl, the core of aripiprazole is 3,4-dihydrocarbostyryl. The linker of aripiprazole is connected to the 7-position carbon atom on the carbostyryl. Because the linker has four methylene groups, (CH₂)₄, it is a butoxy group. Aripiprazole has two substituents on the phenyl in its phenylpiperazine group: a chlorine on the second carbon and a chlorine on the third carbon. Aripiprazole therefore is said to have a 2,3-dichloro substitution on its phenyl ring. Aripiprazole

would be a 7-isomer to a compound having the same configuration except having a linker connected to a carbon atom other than the 7-position on the carbostyryl.

36. Claim 17 reads:

17. The pharmaceutical composition of claim 16, wherein the carbostyryl compound or salt thereof is 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydrocarbostyryl.

37. A carbostyryl compound is a compound that shares the carbostyryl ring system as shown above. When there is a double bond between the third and fourth carbon atoms in the carbostyryl, the result is simply a carbostyryl (or also 3,4 dehydrocarbostyryl). When there is no double bond, the result is a 3,4-dihydrocarbostyryl. Both versions are referred to generally as carbostyryls.

38. Claim 16, from which claim 17 depends reads:

16. A pharmaceutical composition for treating schizophrenia containing, as the active ingredient, a carbostyryl compound or pharmaceutically acceptable salt thereof of claim 1 and a pharmaceutically acceptable carrier.

39. Thus, rewritten in independent form claim 17 reads:

17. A pharmaceutical composition for treating schizophrenia containing, as the active ingredient, the carbostyryl compound 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydrocarbostyryl [aripiprazole] or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

40. Claim 23 reads:

23. The method of treating schizophrenia of claim 22, wherein the carbostyryl compound or salt thereof is 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydrocarbostyryl or a salt thereof.

41. Claim 22, from which claim 23 depends reads:

22. A method of treating schizophrenia in a patient comprising administering a pharmaceutical composition to said patient

containing, as an active ingredient, a carbostyryl compound or salt thereof of claim 1.

42. Thus, rewritten in independent form claim 23 reads:

23. A method of treating schizophrenia in a patient comprising administering a pharmaceutical composition to said patient containing, as an active ingredient, the carbostyryl compound 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydrocarbostyryl [aripiprazole] or salt thereof of claim 1.

2. Prosecution History

43. On October 31, 1988, a few months after the '416 patent issued, Otsuka filed Japanese patent application JP 63-276953 directed to the 7-isomer series of the carbostyryl compounds disclosed in the '416 patent family.

44. The application that issued as the '528 patent (the "'719 application") was filed on October 20, 1989, and claims priority to Otsuka's October 31, 1988 Japanese application.

45. The '719 application was drafted through a collaborative effort between Dr. Yasuo Oshiro, a named inventor, and Dr. Minamikawa, another member of Otsuka's IP Department. In particular, Dr. Oshiro worked with Dr. Minamikawa in drafting the background section of the patent.

46. During prosecution of the '719 application, Dr. Oshiro signed and submitted a declaration to the USPTO in which he represented:

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, § 1.56(a).

....

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

47. The '719 application provided the following description of the prior art:

Among carbostyryl derivatives known in prior art, those disclosed in U.S. Patent No. 4,734,416; Canadian Patent No. 1,117,110; British Patent No. 2,017,701; German Patent Nos. 2,911,108, 1,912,105 and 2,953,723; Japanese Patent Kokai (Laid-open) Nos. 54-130,587 (1979), 55-127,371, (1980) and 62-149,664 (1987) are having chemical structural formulas of upper conception of carbostyryl derivatives of the present invention.

Furthermore, carbostyryl derivatives disclosed in U.S. Patent No. 4,234,585 and European Patent No. 226,441 have chemical structural formula similar to that of carbostyryl derivatives of the present invention, but the pharmacological activities thereof are different from those of possessed by the carbostyryl derivatives of the present invention.

In addition to the above, the carbostyryl derivatives disclosed in U.S. Patent No. 4,234,584 have chemical structural formula similar to that of carbostyryl derivatives of the present invention and also have pharmacological activities similar to those of shown by carbostyryl derivatives of the present invention.

48. During prosecution of the '719 application, the patent examiner rejected the pending claims based on an earlier Otsuka patent, U.S. Patent No. 4,824,840 (the "Banno '840 patent").

49. In response to the rejection, Dr. Oshiro submitted a declaration in which he represented that "he conducted pharmacological tests to show whether carbostyryl derivatives of the ['719] application have excellent anti-apomorphine activity and anti-epinephrine activity over those of performed by compounds of the prior art references." Dr. Oshiro told the PTO in his declaration that "the test were conducted by procedures similar to those employed in

Pharmacological Tests disclosed on pages 27-28 of the specification of the above-identified application.” Dr. Oshiro then set forth the specific test methods purportedly employed.

50. Dr. Oshiro testified, however, that he did not actually perform the tests, and that he does not know who performed them. He testified that Dr. Minamikawa provided him with the declaration to sign

51. The '719 application was allowed following submission of Dr. Oshiro's declaration.

52. On August 11, 2004, prior to commencing this litigation, Otsuka filed with the PTO a request for reexamination of the '528 patent. A reexamination is a process whereby a third party or inventor can have a patent reexamined by a patent examiner to verify that the subject matter it claims is patentable.

53. Otsuka's reexamination request alleged that it could be argued that at least six substantial new questions of patentability may exist based on certain prior art references, including the '416 patent and its German counterpart DE 2,912,105 (“DE '105”). With regard to these two patents, Otsuka noted that they were believed to be “less relevant” than the other listed patents.

54. During the reexamination of the '528 patent, the attorneys at the Finnegan Firm informed the reexamination examiner of “inadvertent errors” in the test results reported in the '528 patent and reported in the Declaration of Y. Oshiro submitted during the original prosecution of the '528 patent. Subsequently, the attorneys at the Finnegan Firm informed the examiner that Otsuka was unable to confirm from the records available that the data reported in the '528 patent and the Declaration of Y. Oshiro was accurate and performed under a common protocol. During the reexamination of the '528 patent, Otsuka submitted the Declaration of

Tsuyoshi Hirose and disavowed further reliance for patentability on the comparative data reported in both the '528 patent and the Declaration of Dr. Oshiro.

55. Dr. Oshiro testified that he did not search for the data for the testing he described in his Declaration.

56. The reexamination examiner repeatedly rejected all the claims of the '528 patent for obviousness based on various items of prior art, including the '416 patent and its European counterparts, including DE '105. As of June 2005, Otsuka's arguments failed to change the examiner's mind, and the PTO issued a final rejection of the claims of the '528 patent.

57. In response to the final rejection, Otsuka submitted the Declaration of Tsuyoshi Hirose, an Otsuka employee (the "Hirose Declaration"). In his Declaration, Dr. Hirose identified four compounds covered by the claims of the '528 patent, and stated: "In my opinion, these four compounds are representative of the carbostyryl compounds claimed in the above-identified U.S. Patent No. 5,006,528." Dr. Hirose also identified four prior art compounds, and stated: "In my opinion, the compounds of the applied references, which are the most structurally similar with carbostyryl derivatives claimed in the above-identified U.S. Patent No. 5,006,528, are those compounds that have a propoxy bridging group, rather than the requisite butoxy bridging group of the claimed compounds." The selected prior art compounds were disclosed and claimed in the '416 patent and its European counterparts, including DE '105.

58. Dr. Hirose testified, however, that he could not identify similarities or differences between the compounds he tested because he did not have knowledge of organic chemistry. He explained that lawyers wrote the Declaration for him, and that he informed attorneys working with him that he did not have a strong background in organic chemistry.

59. After receiving the Hirose Declaration, the reexamination examiner confirmed the patentability of the claims of the '528 patent

E. Claims 12, 17, and 23 of the '528 Patent Are Invalid

1. The Person Having Ordinary Skill in the Art

60. Research in this field, including Otsuka's approach to antipsychotic drug development, was typically done in teams that included expertise in both medicinal chemistry and pharmacology. Such multi-disciplinary teams were typically led by someone with a Ph.D. or an M.D. Such a team so led provides a definition for the level of ordinary skill in the art.

61. If one were to define the hypothetical "person" of ordinary skill in the art as a single individual, the following definition would apply. The person of ordinary skill in the art to whom the '528 patent is directed is an organic chemist, medicinal chemist, pharmacologist, or scientist in a related field that studies antipsychotic drugs, having at least a Ph.D., or equivalent, and at least several years of experience in designing, synthesizing, and/or testing drug compounds. The amount of post-graduate experience depends upon the level of formal education, and particular experience with drugs for the treatment of schizophrenia. One of ordinary skill would also have the knowledge not only in one or more specified areas listed above but also in adjacent fields—*e.g.*, a medicinal chemist would also have a understanding of pharmacology, and vice-versa. One of ordinary skill in the art would have consulted with a pharmacologist when appropriate.

2. Claims 12, 17, and 23 of the '528 Patent Are Invalid for Obviousness-Type Double Patenting

62. Claims 12, 17, and 23 of the '528 patent are invalid for obviousness-type double patenting based on claims 13 and 30 of the '416 patent.

a. The '416 Patent

63. The '416 patent issued on March 29, 1988, more than one year prior to October 20, 1989, the U.S. filing date of the '528 patent. It is therefore prior art to the '528 patent under 35 U.S.C. § 102(b). Contrary to Plaintiff's contentions, the obviousness-type double-patenting analysis is not subsumed in the obviousness analysis merely because the '416 patent is prior art.

64. The '416 patent expired on March 29, 2005.

65. The '528 patent was set to expire on October 20, 2009 but was granted a 5-year term extension and will therefore expire on October 20, 2014.

66. Both the '416 and '528 patents were applied for and issued to Otsuka and are presently owned by Otsuka.

67. In addition to listing the '416 patent in the Orange Book as covering aripiprazole, Otsuka also represented in the Abilify package insert and in NDA No. 21-436 that the '416 patent covered aripiprazole.

68. The '416 and '528 patents have a common inventor. The named inventors of the '416 patent are Kazuo Banno, Yasuo Oshiro, and Kazuyuki Nakagawa. The named inventors of the '528 patent are Yasuo Oshiro, Seiji Sato, and Nobuyuki Kurahashi.

69. The '416 patent states that "compounds of the present invention are useful for central nervous controlling agents such as . . . antischizophrenia agents." Col. 3, ll. 13-16. The '416 patent describes a number of animal models that could indicate antipsychotic activity, such as "apomorphine-vomiting inhibitory action," "spontaneous movement controlling actions," "hypermotion controlling action of rat," "methamphetamine group toxicities lowering action," and "anti-methamphetamine action." In addition, the '416 patent teaches that the disclosed compounds have "weak activities" in models indicative of side effects of antischizophrenic drugs, such as "anticholine action" and "catalepsy inducing action," and do not show side effects

of Parkinsonism or tardive dyskinesia. In an interference proceeding before the PTO involving the patent application for the '416 patent, Otsuka submitted expert testimony for the proposition that all of the compounds encompassed within the general formula of the '416 patent have both antihistaminic and central nervous controlling effect.

70. Claim 13 of the '416 patent reads:

13. 7-{4-(4-phenylpiperazinyl)butoxy}-3,4-dihydrocarbostyryl.

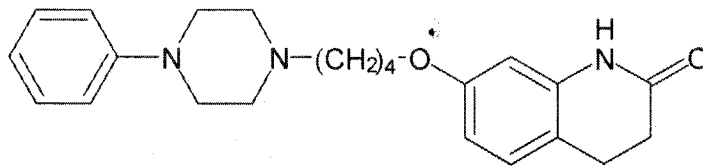
This compound is known as the "unsubstituted butoxy." The unsubstituted butoxy is identical to aripiprazole except for the fact that aripiprazole has chlorine atoms at the 2 and 3 positions of the phenyl ring and the unsubstituted butoxy has hydrogen atoms at those positions.

71. The claims of the '416 patent also include the Otsuka compounds known as OPC-4392 and OPC-4139, which are further discussed in the section on obviousness.

b. Subject Matter of Claims 12, 17, and 23 of the '528 Patent Is Not Patentably Distinct from the Subject Matter of Claim 13 of the '416 Patent

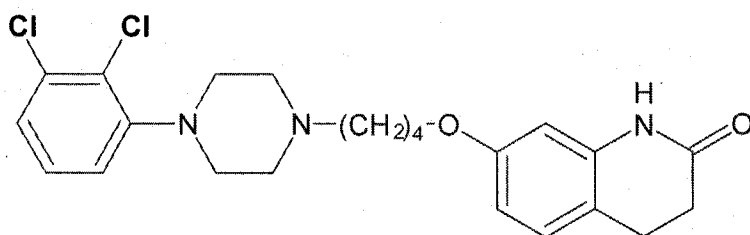
72. The unsubstituted butoxy of claim 13 of the '416 patent differs from aripiprazole (claim 12 of the '528 patent) only in that it does not have the chlorine substituents on the 2 and 3 positions of the phenyl ring.

73. A comparison of the molecules is shown below.



7-[4-(4-phenylpiperazinyl)butoxy]-3,4-dihydrocarbostyryl ("unsubstituted butoxy")





7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostryl (“aripiprazole”)

74. Claim 13 of the '416 patent additionally differs from Claim 17 of the '528 patent in that claim 13 does not include a pharmaceutically acceptable carrier.

75. Claim 13 of the '416 patent additionally differs from claim 23 of the '528 patent in that claim 13 is not drawn to a method of treating schizophrenia.

76. The asserted claims are not patentably distinct from claim 13 of the '416 patent in light of the declaration of Otsuka employee Kazuyuki Nakagawa (the “Nakagawa Declaration”), which was submitted during prosecution of the '416 patent.

77. At the time he submitted his declaration, Dr. Nakagawa was the head of the synthesis division of the project that developed central nervous system drugs at Otsuka. Dr. Oshiro, who is an inventor on both the '416 and '528 patents, worked under the direction of Dr. Nakagawa.

78. Otsuka submitted the Nakagawa Declaration in order to convince the patent examiner to allow the '416 patent to issue. It contains data from animal testing performed by Otsuka on a number of carbostryl compounds, which were intended to supplement the data in the specification.

79. One of the tests described in the Nakagawa Declaration is known as “the mouse jumping test.” The mouse jumping test was used at that time, and is still used, by researchers in the field as a screening test to determine whether a compound has antischizophrenic activity. In particular, activity in the mouse jumping test was recognized in the art as a measure of positive

symptom treatment. Activity in the mouse jumping test strongly correlates with antischizophrenic activity.

80. Otsuka itself regularly used the mouse jumping test to screen compounds for antischizophrenic activity. Moreover, for the application that resulted in U.S. Patent No. 4,619,932, Otsuka used the results of the mouse jumping test to convince the patent examiner that the claims at issue had antischizophrenic activity. Otsuka described the mouse jumping test as a “method for determining whether a compound will [have] anti-schizophrenic activity” and represented to the examiner that activity in the mouse jumping test provides “reasonable assurance” that a compound has antischizophrenic activity.

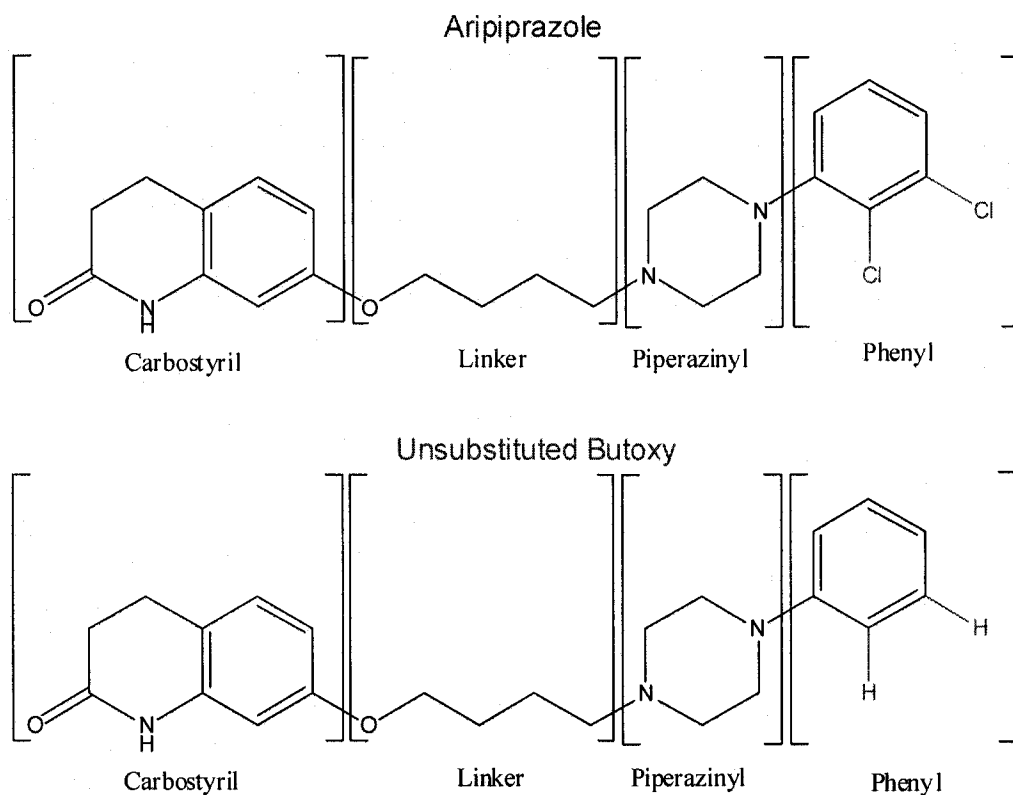
81. The Nakagawa Declaration reports mouse jumping data for nine of the compounds disclosed in the '416 patent. One of the compounds was the unsubstituted butoxy, which is the subject matter of claim 13 of the '416 patent.

82. The mouse jumping data in the Nakagawa Declaration include a head-to-head comparison between the unsubstituted *propoxy* carbostyryl compound and the unsubstituted *butoxy* compound. A lower score in the mouse jumping test indicates greater antischizophrenic potency. The propoxy compound had a score of 9.3 and the *butoxy* compound had a score of 5.5, indicating the butoxy compound had greater antischizophrenic activity.

83. The Nakagawa Declaration therefore teaches that antischizophrenic activity increases when a butoxy linker is substituted for a propoxy linker.

84. As described above, the only difference between aripiprazole and the unsubstituted butoxy is at the 2 and 3 positions of the phenyl group. Aripiprazole has chlorine atoms at those positions, whereas the unsubstituted butoxy has hydrogen atoms at those positions.

85. One of ordinary skill would have considered chlorine substituents on the phenyl ring to be routine, predictable, automatic, and almost inevitable variations of an unsubstituted phenyl ring.



86. The prior art taught that hydrogens on the phenyl group could be replaced with other substituents to increase activity. Chlorine was commonly used as a substituent. In fact, chlorine substitution was often the first substitution made in CNS drug development because of steric effects, electronic effects, and lipophilicity. "Steric" relates to or involves the arrangement of atoms in space, so steric effects refer to the effects that the arrangement of the substituents may have on the molecule's shape and reactivity. Chlorine substitution increases steric bulk somewhat and causes some polarization (i.e., charge) due to its electronegative nature, which in turn frequently enhances a compound's biological activity, especially in CNS agents.

Lipophilicity refers to the ability of a chemical compound to dissolve in, among other things, fats and oils. Lipid soluble molecules are able to penetrate through the blood-brain barrier relatively easily via the lipid membranes of the cells. Thus, enhanced lipophilicity enhances a molecule's ability to penetrate the blood-brain barrier, which can result in the increased activity of a drug.

87. Further, the prevailing belief among researchers in the field in 1988 was that one needed an electron-withdrawing substituent, such as chlorine, on the phenyl ring in order to obtain good antischizophrenic potency.

88. The data from the Nakagawa Declaration is consistent with, and supports, the expectation of one of ordinary skill in the art that the chlorine substitution generally improves the potency of an antischizophrenic compound. Compound 39 of the Nakagawa Declaration which has chlorine at position 3 on the phenyl group, and Compound No. 43 of the Nakagawa Declaration, which has chlorine at position 2 on the phenyl group showed greater activity than the unsubstituted propoxy compound. The data in the Nakagawa Declaration would have therefore strongly suggested to the person of ordinary skill in the art that adding chlorine at the 2 and/or 3 position of the phenyl group would increase antischizophrenic potency.

89. One of ordinary skill would have expected the effects of substituents to be additive and that adding two chlorines would have an equal or enhanced effect over a single chlorine substitution.

90. Adding chlorine at both the 2 and 3 positions of the phenyl ring was known in the prior art and would have been only a small next step for the person of ordinary skill. Example 317 of the DE '105 patent (the German counterpart to the '416 patent) has chlorines at both positions 2 and 3 and differs from aripiprazole in that it has a propoxy linker instead of a butoxy linker. Similarly, Swedish Patent Application No. 434,945 discloses the 2,3-dichloro propoxy

compound and its utility as an antischizophrenic agent. Other compounds having antipsychotic activity also include the 2,3, dichloro substitution. Example 3 of the '456 patent shows the coumarin analog of the DE '105 Example 317.

91. Double patenting does not require inquiry into a motivation to modify the prior art. Even if it did, however, the data in the Nakagawa Declaration would have motivated the person of ordinary skill in the art to substitute chlorine for hydrogen, and to do so at positions 2 and 3 of the phenyl ring. In addition, one of skill would have expected that such a substitution would have resulted in a compound having stronger antischizophrenic potency. Further, there is no prior art teaching that teaches or suggests that making such a substitution on the phenyl ring would have eliminated the antischizophrenic activity of a carbostyryl derivative.

92. Given the data in the Nakagawa Declaration regarding chlorine substitution at the 4 position and Otsuka's prior art compounds OPC-4392 and OPC-4139, the person of ordinary skill would have readily envisioned aripiprazole, which is a 2,3-dichloro substituted compound. Aripiprazole would certainly have been one of the no more than a handful of compounds contemplated by the person of ordinary skill in the art based on the Nakagawa Declaration.

93. One of ordinary skill in the art would have known how to make aripiprazole.

94. The data in the Nakagawa Declaration would have motivated the person of ordinary skill in the art to substitute chlorine for hydrogen, and to do so at positions 2 and 3 of the phenyl ring. In addition, one of skill would have expected that such a substitution would have resulted in a compound having stronger antischizophrenic potency. Further, there is no prior art teaching that teaches or suggests that making such a substitution on the phenyl ring would have eliminated the antischizophrenic activity of a carbostyryl derivative.

95. Contrary to Plaintiff's contention, the Nakagawa Declaration is prior art. The Nakagawa Declaration, which Otsuka submitted during the prosecution of the application that led to the '416 patent in order to convince the patent examiner to allow the application to issue as the '416 patent, is prior art. The prosecution history of the '416 application was publicly accessible as of the issuance of the '416 patent, March 29, 1988, more than one year prior to the filing of the application that led to the '528 patent. The '416 patent states that the claimed compounds are useful as "antischizophrenia agents" and would therefore have allowed one of ordinary skill in the art to locate its prosecution history, including the Nakagawa Declaration. Further, the '416 patent is indexed and classified and the person of ordinary skill in the art would have been able to locate its prosecution history, including the Nakagawa Declaration. Persons of ordinary skill in the art would have considered the teachings of the Nakagawa Declaration. The Nakagawa Declaration is therefore a printed publication.

96. Not only was the Nakagawa Declaration accessible to the public upon issuance of the '416 patent, but both Otsuka and its law firm, Finnegan, are estopped from denying that they were aware of the Nakagawa Declaration during prosecution of the '528 patent. Specifically, Dr. Oshiro is a named inventor on both the '416 and '528 patents. The Finnegan firm represented Otsuka during prosecution of both patent applications that led to the issuance of the '416 and '528 patents. In other words, the Finnegan firm oversaw the decision to submit, the preparation of, and the submission of the Nakagawa Declaration to the PTO. As such, the Finnegan firm knew that, upon issuance, the entire prosecution history of the '416 patent, including the Nakagawa Declaration, would be publicly available. This is not a situation where prior art is available to the public but is unknown to either Otsuka or Finnegan or can't be accessed through a reasonable search of the PTO records.

97. Additional prior art, such as the work relating to Otsuka's compounds OPC-4392 and OPC-4139 is discussed *infra* in connection with obviousness, also supports the motivation of the person of ordinary skill to replace the hydrogens at the 2 and 3 positions of the phenyl group with chlorines and the expectation that such a change would have led to a compound having increased antischizophrenic activity.

98. Secondary considerations do not apply to the obviousness-type double-patenting analysis.⁶ Even if secondary considerations were considered, paragraphs 170–219 below demonstrate that secondary considerations do not support a finding of nonobviousness.

99. One of ordinary skill in the art would have known how to make aripiprazole.

100. As described above, based on the teachings of the Nakagawa Declaration and other prior art, the person of ordinary skill in the art would have been motivated to substitute the hydrogen atoms at the 2 and 3 positions of the phenyl ring in the molecule of claim 13—the unsubstituted butoxy—with chlorine atoms and would have had an expectation that the resulting molecule (aripiprazole) would have excellent antischizophrenic activity.

101. One of ordinary skill would have considered chlorine substituents on the phenyl ring to be routine, predictable, automatic, and almost inevitable variations of an unsubstituted phenyl ring.

102. Based on the teachings of the Nakagawa Declaration, the person of ordinary skill in the art would have expected the antischizophrenic activity of aripiprazole to have been as good as or better than that of the unsubstituted butoxy.

⁶ *Procter & Gamble Co. v. Teva Pharmaceuticals USA, Inc.*, 566 F.3d 989, 998 (Fed. Cir. 2009) (“[D]ouble patenting does not require an inquiry into objective criteria suggesting non-obviousness.”) (citing *Geneva Pharm., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1378 (Fed. Cir. 2003)).

103. The person of ordinary skill in the art would therefore have been motivated to use aripiprazole or one of its pharmaceutically acceptable salts as the active ingredient in a pharmaceutical composition to treat schizophrenia together and would have had a reasonable expectation of success in doing so.

104. Therefore, aripiprazole is an obvious variant of and not patentably distinct from the unsubstituted butoxy.

**c. The Subject Matter of Claims 12, 17, and 23 of the '528 Patent
Is Not Patentably Distinct from the Subject
Matter of Claim 30 of the '416 Patent**

105. Claim 30 of the '416 patent covers a genus of phenylpiperazine carbostyryl compounds, in which two of the hydrogens in the phenyl group are replaced with halogen atoms, including chlorine. It reads:

30. The compound of claim 1 wherein R⁵ is a phenyl group substituted by two halogen atoms.

106. Claim 30 covers aripiprazole.

107. Based on the Nakagawa declaration and the literature on OPC 4392 and OPC 4139, as discussed above, the person of ordinary skill in the art would have recognized aripiprazole as one of the molecules within the genus of claim 30 and would have had a reasonable expectation that it would have excellent antischizophrenic activity.

108. The person of ordinary skill in the art would have been motivated to use aripiprazole or one of its pharmaceutically acceptable salts to treat schizophrenia and would have had a reasonable expectation of success.

109. Therefore, one of ordinary skill would have recognized that aripiprazole is an obvious variant of, and not patentably distinct from, the class of compounds recited in claim 30 of the '416 patent.

110. Secondary considerations do not apply to the obviousness-type double-patenting analysis.⁷ Even if secondary considerations were considered, paragraphs 170-219 below demonstrate that secondary considerations do not support a finding of nonobviousness.

3. The Subject Matter of Claims 12, 17, and 23 of the '528 Patent Would Have Been Obvious to the Person of Ordinary Skill in the Art at the Time the Invention Was Made

a. The Scope and Content of the Prior Art

111. The prior art includes at least the following:

- a. U.S. Patent No. 4,734,416 and its prosecution history, including the Nakagawa Declaration. (DTX-6, DTX-214, & DTX-247.)
- b. U.S. Patent No. 4,619,932 and its prosecution history. (DTX-20 and DTX-1147.)
- c. German Patent DE 29 12 105 C2. (DTX-248.)
- d. Shinbo, "An Overview of Antipsychotic and Antidepressant Drugs," Toyaku Zasshi, Vol. 10, No. 10 (1988). (DTX-1169 & DTX-1169T.)
- e. Murasaki et al., "Phase 1 Study of OPC-4392," Prog. Neuro-Psychopharmacol. and Biol. Psychiat., 12, pp. 793-802 (Sept. 20, 1988). (DTX-874.)
- f. Sasa et al., "Presynaptic Inhibition of Excitatory Input from the Substantia Nigra to Caudate Nucleus Neurons by a Substituted Quinolinone Derivative 7-{3-[4-(2,3-dimethylphenyl)piperazinyl]propoxyl}-2[1H]-quinolinone," Life Sci. 43, pp. 263-69 (1988). (DTX-900.)
- g. Wise, et al., "7-[3-(Aryl-1-Piperazinyl) Propoxy]-2H-1-Benzopyran-2-Ones. A New Class Of Dopamine Autoreceptor Agonist," poster presented at the November 1987 Meeting of the Society for Neuroscience in New Orleans (the "1987 Wise Poster"). (DTX-398.)
- h. Gerbaldo et al., "Treatment of Negative Symptoms of Schizophrenic Patients with the Partial Dopamine Agonistic Compound OPC-4392," Psychopharmacology, Vol. 96, Supp. 1, p. 238 (March 1988) (Abstract). (DTX-990.)

⁷ *Procter & Gamble Co. v. Teva Pharmaceuticals USA, Inc.*, 566 F.3d 989, 998 (Fed. Cir. 2009) ("[D]ouble patenting does not require an inquiry into objective criteria suggesting non-obviousness.") (citing *Geneva Pharm., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1378 (Fed. Cir. 2003)).

i. Murasaki, "New Psychoneurological Agents," Japanese J. of Clinical Psychiatry, Vol. 16, No. 11, pp. 1515-1527 (1987). (DTX-388 & DTX-388T.)

j. Murasaki, et al., "Phase 1 Study of OPC-4392," Clin. Eval. 16, pp. 149-195 (March 1988). (DTX-875 and DTX-875T.)

k. Nakagawa, et al., "Derivatives of 3,4-Dihydrocarbostyrils of β -Adrenergic Blocking Agents," Journal of Medicinal Chemistry, 17(5), pp. 529-533 (1974). (DTX-383.)

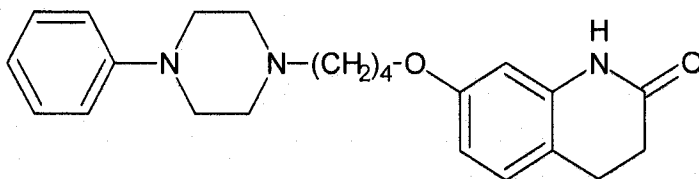
l. Hiyama et al., "Neuropharmacological Actions of 7{3-[4-(3-chlorophenyl)piperazinyl]propoxy} 3,4-dihydro-2(1H)-quinolone (OPC-4139)," (excerpt), Eighth Int'l Cong. Pharmacol., Abstracts (1981). (DTX-514).

m. U.S. Patent 4,701,456. (DTX 629).

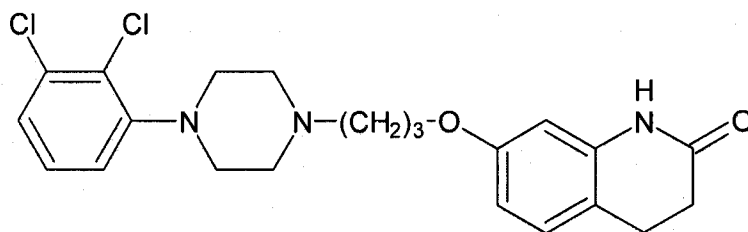
b. The Differences Between the Prior Art and the Claimed Invention

112. The prior art discloses at least the following compounds that are structurally similar to aripiprazole and their activity and use as anti-schizophrenic agents:

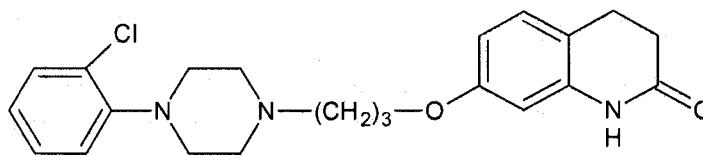
a. 7-{4-(4-phenylpiperazinyl)-butoxy}-3,4-dihydrocarbostyryl ("unsubstituted butoxy"), which has the following structural formula:



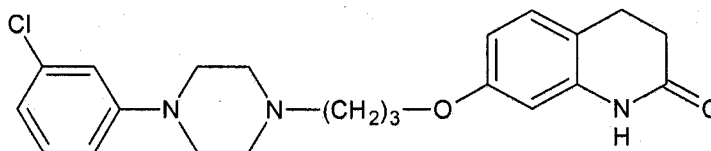
b. 7-{3-[4-(2,3-dichlorophenyl)-1-piperazinyl]-propoxy}-3,4-dihydrocarbostyryl ("2,3-dichloro propoxy"), which is a homolog of aripiprazole and has the following structural formula:



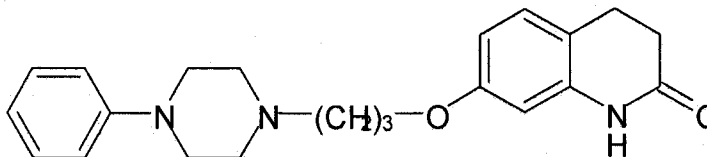
c. 7-{3-[4-(2-chlorophenyl)-1-piperazinyl]-propoxy}-3,4-dihydrocarbostyryl ("2-chloro propoxy"), which has the following structural formula:



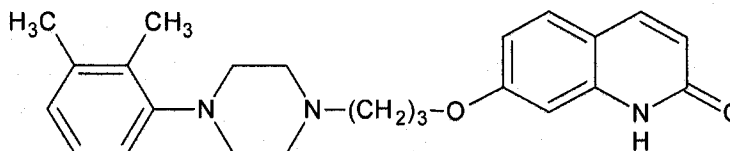
- d. 7-{3-[4-(3-chlorophenyl)-1-piperazinyl]-propoxy}-3,4-dihydrocarbostyryl ("3-chloro propoxy" or "OPC-4139"), which has the following structural formula:



- e. 7-{3-[4-phenyl)-1-piperazinyl]-propoxy}-3,4-dihydrocarbostyryl ("unsubstituted propoxy"), which has the following structural formula:



- f. 7-{3-[4-(2,3-dimethyl)phenyl)-1-piperazinyl]-propoxy}-carbostyryl ("OPC-4392"), which has the following structural formula:



113. The unsubstituted butoxy differs from aripiprazole only in that aripiprazole has chlorine atoms instead of hydrogen atoms at the 2 and 3 positions of the phenyl ring.

114. The 2,3-dichloropropoxy differs from aripiprazole only in that aripiprazole has a butoxy linker instead of a propoxy linker.

115. The 2-chloro propoxy differs from aripiprazole in that aripiprazole has a butoxy linker rather than a propoxy linker and has a chlorine, instead of a hydrogen atom, at the 3 position of the phenyl ring.

116. The 3-chloro propoxy (or OPC-4139) differs from aripiprazole in that aripiprazole has a butoxy linker rather than a propoxy linker and has a chlorine, instead of a hydrogen atom, at the 2 position of the phenyl ring.

117. The unsubstituted propoxy differs from aripiprazole in that aripiprazole has a butoxy linker rather than a propoxy linker and has chlorine atoms, instead of hydrogen atoms, at the 2 and 3 positions of the phenyl ring.

118. OPC-4392 differs from aripiprazole in that aripiprazole has a butoxy linker rather than a propoxy linker, has chlorine atoms, instead of methyl groups, at the 2 and 3 positions of the phenyl ring, and has a single bond instead of a double bond connecting carbons 3 and 4 of the carbostyryl group.

119. The 2,3 dichloro coumarin differs from aripiprazole in that aripiprazole has a butoxy linker rather than a propoxy linker, has an NH group instead of an O in the heterocyclic half of the bicyclic structure, and has a single bond instead of a double bond at the 3,4-position of the bicyclic structure.

c. The Claimed Invention Would Have Been Obvious to the Person of Ordinary Skill in the Art

120. The unsubstituted butoxy and 2,3-dichloro propoxy prior art compounds bracket aripiprazole. Based on the Nakagawa Declaration and other prior art one of ordinary skill in the art would have been motivated to and would have known how to modify them to make

aripiprazole. Based on the Nakagawa declaration, the '932 patent file history and the 2,3-dichloro propoxy coumarin the person of ordinary skill would have proceeded with the reasonable expectation that the compound would have antischizophrenic activity. The bracketing of aripiprazole arises from the fact the 2,3-dichloro propoxy is a homolog of aripiprazole and thus only differs from aripiprazole in the length of the linker, and the unsubstituted butoxy *does* include the same butoxy linker of aripiprazole but is unsubstituted at the phenyl ring. Structurally similar compounds, including homologs, give rise to the presumption that they will have similar properties. In fact, it had been long known that homologation was the simplest possible change to make to a molecule in medicinal chemistry, where the results of such a change would be expected to be to the level of potency, but not the type of activity. The person of ordinary skill in the art would have known how to make aripiprazole and would have expected it to have better antischizophrenic potency than the unsubstituted butoxy or 2,3-dichloro propoxy.

d. One of Skill in the Art Would Have Been Motivated to Select the Unsubstituted Butoxy and OPC-4392 as Lead Compounds and Modify Them to Arrive at Aripiprazole

121. Defendants submit that any requirement that an obviousness challenge begin with the identification of a "lead compound" to the exclusion of other compounds in the prior art is inconsistent with a long line of Federal Circuit precedent. To the extent this Court believes that the selection of a lead compound is required, however, the person of ordinary skill in the art would have selected the unsubstituted butoxy and OPC-4392 as lead compounds for the reasons discussed below.

122. By 1988, the person of ordinary skill in the art would have considered a compound with an excellent safety profile that could treat the positive and negative symptoms of

schizophrenia with minimal EPS liability and low liability for increasing prolactin levels a promising and natural choice for further development. The person of ordinary skill would have considered a compound that could be modified to have such a profile or that would likely have a similar profile a promising and natural choice for further development. Persons of ordinary skill in the art would have considered promising and a natural choice for further development a compound from a class of compounds that had been demonstrated clinically to have a potential for the desired activity profile and also appeared to have no potentially serious side effects.

The '416 patent and its European counterparts, the Nakagawa Declaration, and publications about OPC-4392 and OPC-4139, among other pieces of prior art, would have motivated one of ordinary skill in the art who was looking to develop an antischizophrenic drug to focus on carbostyryl derivatives. The '416 patent and its European counterparts would have taught one of ordinary skill in the art that carbostyryl derivatives were potential antischizophrenic agents with a low liability for side effects. The Nakagawa Declaration would have taught one of ordinary skill in the art that many of the carbostyryl derivatives had "excellent" antischizophrenic potency. The prior art taught that atypical antischizophrenics were potentially available in every structural family of antischizophrenic candidate drugs, suggesting that an atypical antipsychotic could be found in the carbostyryl family. In particular, the publications about OPC-4392 and OPC-4139 would have taught to one of ordinary skill in the art that some carbostyryl derivatives had or could be expected to have the profile of an atypical antipsychotic.

123. The treatment of negative symptoms was in particular a considerable hurdle in development of antischizophrenia agents. By 1988, animal models were sufficiently predictive of the treatment of the positive symptoms of schizophrenia, but were hardly predictive of the treatment of the negative symptoms. Thus, focusing on a class of compounds, such as the

carbostyryl derivatives, shown to have the desired activity in animal models on the positive symptoms, and at least one compound of which was shown in a clinical study to have activity on the negative symptoms with minimal EPS, would have been considered by one of ordinary skill in the art to be a more promising avenue to explore than trying to make structural changes to other compounds in an attempt to discover activity to treat negative symptoms and eliminate EPS and other serious side effects.

124. The person of skill in the art would have looked to the claims of the '416 patent and its foreign counterparts to gain an understanding of what compounds Otsuka considered to be important and most promising for development. The unsubstituted butoxy is recited by itself in claim 13 of the '416 patent. The unsubstituted butoxy is also encompassed by the subgenus of compounds covered by claim 80 of the '416 patent, which is directed to a composition having an antihistaminic and a central nervous controlling effect.

125. The person of ordinary skill in the art would have also looked at the selection of compounds assayed in the mouse jumping test in the Nakagawa Declaration to gain an understanding as to what compounds the inventors of the '416 patent considered to be promising antischizophrenic agents. One of skill in the art would have considered the unsubstituted butoxy as an excellent medicinal chemistry lead compound to submit to SAR studies since it had no substituents on its phenyl group. Further, the unsubstituted butoxy would have stood out from the compounds tested in the mouse jumping test because it was the only butoxy-linked compound and, based on the mouse jumping data, the person of ordinary skill would have had an expectation that butoxy-linked compounds would have increased antischizophrenic potency over propoxy-linked compounds.

126. Thus, based at least on the teachings of the '416 patent and the Nakagawa Declaration, one of ordinary skill in the art would have been motivated to select the unsubstituted butoxy as a lead compound.

127. In addition, based at least on the discussions below, one of ordinary skill would have been motivated to select OPC-4392, another 7-isomer carbostyryl derivative, as a lead compound.

128. Given the state of the art in 1988, a person of ordinary skill in the art would have focused on the carbostyryl derivatives described in the '416 patent and Nakagawa Declaration, rather than those described in U.S. Patent No. 4,619,932 (the "'932 patent") and JP 58-203968 ("JP '968"). The '932 patent was filed on March 9, 1983, and issued on October 28, 1986. JP '968 was filed on May 21, 1982, and was published on November 28, 1983. The Nakagawa Declaration was submitted several years later on February 2, 1987, and became prior art as of March 29, 1988, when the '416 patent issued. In 1988, the person of ordinary skill in the art would have considered the '416 patent and Nakagawa Declaration to provide further direction as to the types of carbostyryl derivatives to pursue as antischizophrenic agents with greater activity on the positive symptoms (since this was the antipsychotic activity being measured by the mouse jumping test).

129. The '932 patent discloses carbostyryl derivatives in which the linker is attached at the 6-position of the carbostyryl group ("6-position carbostyryl derivatives") and the linker is composed of a hydrocarbon (carbon-carbon) chain rather than an alkoxy chain. The '932 patent provides test results for 6-position carbostyryl derivatives for "activity for antagonizing epinephrine in mouse," which indicates that these compounds have potent alpha-blocking activity and thus the potential to cause unwanted cardiovascular side effects. This was at its

worst for 2-ethoxy compounds where the therapeutic index (good numbers high) was under 0.1, as compared to a therapeutic index slightly over 1 for chlorpromazine, a drug known to have orthostatic hypotension as a side-effect. In particular, it would give a person of ordinary skill in the art pause regarding the 5-isomer with the ethoxy in the Nakagawa Declaration. Also, the 5-isomer compounds raised the issue of whether the 5-isomer compounds might have the same problem as the 6-isomer compounds.

130. Further, the '932 patent and JP '968 do not criticize, discredit, or otherwise discourage investigation into a 7-position unsubstituted carbostyryl derivative with a butoxy linker.

131. The Nakagawa Declaration did not include 6-position carbostyryl derivatives to demonstrate activity in the anti-methamphetamine mouse jumping test—*i.e.*, antischizophrenic activity. Dr. Nakagawa is one of the named inventors on the '932 patent and, as such, was already familiar with the results of testing on 6-position carbostyryl derivatives. Now, in order to demonstrate the superiority in antischizophrenic activity of his compounds sought to be patented in the '416 patent, Dr. Nakagawa avoided the 6-position carbostyryl derivatives and selected only 5-position carbostyryl derivatives and 7-position carbostyryl derivatives for testing.

132. One of ordinary skill in the art therefore would have concluded from the Nakagawa Declaration that compounds substituted at the 5- and 7-position (not at the 6-position) were those that the inventors including Dr. Nakagawa considered to most strongly support the claim of antischizophrenic activity and were thus of most interest as antischizophrenic agents at the time.

133. While some 5-isomer carbostyryl compounds were included in the Nakagawa Declaration, the person of ordinary skill in the art would have focused on the 7-isomers. First, OPC-4392, which had already been clinically tested and was shown to have antischizophrenic

activity without orthostatic hypotension or EPS side-effects in clinical studies, especially with regard to negative symptoms, was a 7-isomer. Second, OPC-4139, on which by 1988 was the only other carbostyryl derivative that Otsuka had published promising pre-clinical antipsychotic results, was also a 7-isomer. OPC-4139 was the second-most extensively tested carbostyryl potential antischizophrenic and found to be potent in suppressing dopaminergic activity without inducing catalepsy. It was also included in the Nakagawa Declaration in 1987, reinforcing its importance. Third, Otsuka had not published any pre-clinical results on 5-isomers, and had not submitted any 5-isomers to clinical testing. Fourth, the literature indicated that 5-isomers could have unwanted cardiovascular effects. The prior art had already established potent compounds with safety problems, so the information about the safety of the 7-isomer compounds OPC-4392 and OPC-4139 would have led a person of ordinary skill in the art to choose the 7-isomer compounds over the 5-isomer compounds. .

134. The '932 patent, JP '968, and the '416 patent share three inventors—Kazuo Banno, Takafumi Fujioka, and Kazuyuki Nakagawa—and the '932 patent and JP '968 predate the Nakagawa Declaration and the prior art relating to the clinical testing of OPC-4392. One of ordinary skill in the art would have taken into account this chronology and concluded the most promising compounds to be the 7-position carbostyryl derivatives with alkoxy linkers, rather than the 6-position carbostyryl derivatives with all-carbon linkers disclosed in the '932 patent or the 6-position carbostyryl derivatives disclosed in JP '968.

135. The prior art also taught away from using a clozapine derivative as a lead compound. While a person of ordinary skill in the art might expect clozapine derivatives to have similar antischizophrenic activity and low liability for EPS, they would also expect this class of compounds to suffer from the same shortcomings—*i.e.* inducing agranulocytosis, seizures, and

orthostatic hypotension. This fact was borne out by findings during clinical trials of clozapine derivatives. Further, by 1988, clozapine derivatives had already been extensively studied and modifying clozapine so as to avoid its side effects, while retaining its activity, had been shown to be for the most part unproductive.

136. For similar reasons, a person of ordinary skill in the art in 1988 would also not have been drawn to derivatives of thioridazine as a lead compound. Thioridazine belongs to the well-studied class of compounds known as phenothiazines, which includes the typical antipsychotic chlorpromazine. This class of compounds was known for the potential to cause EPS symptoms as well as serious cardiovascular side effects.

137. While by 1988 risperidone appeared to have the desired activity and safety profile in preliminary preclinical and clinical reports, a person of ordinary skill would not have limited her considerations of lead compounds to only this class of compounds based on such early data.

138. The teachings of the prior art as a whole, therefore, would have directed and motivated a person of skill in the art to select OPC-4392 and the unsubstituted butoxy as lead compounds for further development.

e. One Of Ordinary Skill Would Have Modified the Unsubstituted Butoxy to Result in Aripiprazole with A Reasonable Expectation of Obtaining a Compound Having Antischizophrenic Activity

139. For at least the reasons discussed in paragraphs 117 - 134, one of skill in the art would have been motivated to select the unsubstituted butoxy as a lead compound for further development. For at least the reasons discussed in paragraphs 66 - 83, one of skill in the art would have been motivated to substitute the hydrogen atoms at the 2 and 3 positions of the phenyl ring on the substituted butoxy and would have an expectation that the resulting molecule

(aripiprazole) would have excellent antischizophrenic potency. One of ordinary skill in the art would also have known how to make aripiprazole.

f. One Of Ordinary Skill Would Have Modified OPC-4392 to Result in Aripiprazole with a Reasonable Expectation of Obtaining a Compound Having Antischizophrenic Activity

140. One of the lead doctors who conducted the original clinical trials of OPC-4392 for Otsuka has published a paper describing the important role that the development of OPC-4392 played in the synthesis of aripiprazole, the so-called “successor of OPC-4392.”

141. Prior to aripiprazole, OPC-4392 was the only carbostyryl compound that Otsuka had subjected to human clinical testing including testing on patients suffering from schizophrenia.

142. Prior to filing for the '528 patent, Otsuka elected to publish information about OPC-4392, including the results of Phase I and II clinical trials in humans. Those publications put OPC-4392 and its clinical trials into the public domain, making it part of the prior art.

143. The prior art reveals that OPC-4392 had a number of favorable characteristics.

144. First, OPC-4392 had some activity in ameliorating the positive symptoms of schizophrenia. For example, it was reported that OPC-4392 had treated humans experiencing hallucinations.

145. Second, OPC-4392 was particularly strong in relieving the negative symptoms of schizophrenia.

146. Third, OPC-4392's side effect profile was good with respect to EPS, blood prolactin levels, and orthostatic hypotension. There was also no indication that patients would develop agranulocytosis from treatment with OPC-4392. Patients sometimes experienced minor

side effects such as nausea, but these effects were not life threatening and did not prevent administration of OPC-4392 to humans.

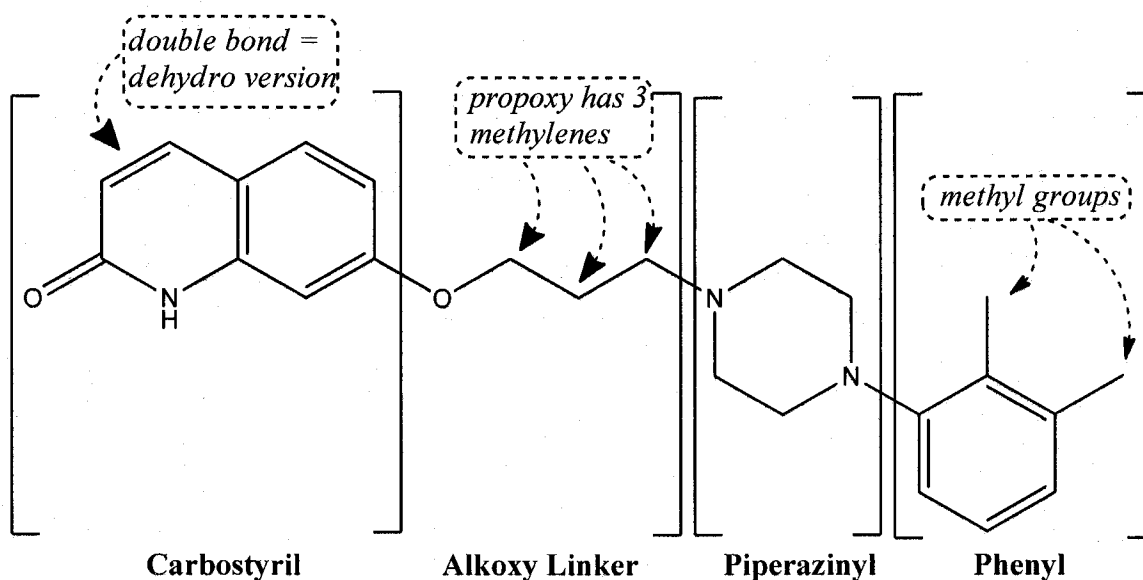
147. OPC-4392 had all the characteristics that those of ordinary skill in the art were looking for in an antischizophrenic drug, save only that its effect on positive symptoms could have been stronger.

148. In October 1988 a person of ordinary skill looking at the publicly reported results of the clinical trials would have concluded that a carbostyryl compound similar to OPC-4392 would likely have the characteristics desired in an antischizophrenic drug. This skilled person would likely have continued to pursue this line of research by selecting for further testing a group of compounds that were variations on the OPC-4392 theme. Such research usually involved testing a group of compounds together, rather than proceeding one compound at a time.

149. The question the skilled person would have faced is what changes should be made to OPC-4392's structure so as to increase positive symptom efficacy without losing the compound's other advantages including relieving the negative symptoms of schizophrenia.

150. To improve the potency of OPC-4392, the skilled person would have chosen to make smaller, less drastic changes before making bigger, more drastic changes. This would have reduced the risk of jeopardizing the retention of the desirable characteristics of OPC-4392. This would have been consistent with the generally accepted approach to modifying a lead compound by making changes that keep close to the structure of the lead before going further afield.

151. OPC-4392 has the following features:



(OPC-4392)

152. In this drawing the left-most group is the carbostyryl group from which this whole class of compounds is given its name. These carbostyryls come in two forms, the double bond version (“dehydro”) and the single bond version (“dihydro”). OPC-4392 is the double bond version as shown by the twin diagonal lines in the upper left portion of the left portion of the carbostyryl group.

153. An alkoxy linker connects the carbostyryl group to the two groups on the right. OPC-4392’s linker group is called a “propoxy” version of an alkoxy linker because of the three CH₂ (“methylene”) groups in it (each CH₂ is implied by a bend in the linker).

154. Piperazinyl and phenyl rings make up the groups on the right. Often they are thought of together as a single group—*i.e.*, a phenylpiperazinyl group.

155. In the drawing for OPC-4392, two lines stick out from the top and top-right of the phenyl ring. These represent CH₃ (“methyl”) substituents attached to that group. These methyl

substituents are attached at the 2 and 3 positions. Thus, OPC-4392 is said to be 2,3 dimethyl substituted.

156. One of the first things a skilled person would have considered doing is changing the length of the linker by adding or subtracting a methylene group. Compounds that differ only by the number of methylene groups in a chain are called “homologs” of each other. Changing to the next highest homolog is a simple change that one of ordinary skill would have considered. The skilled person would have considered the likely effect of changing the length of the linker.

157. The question would have been whether to add or subtract methylene groups and how many. As discussed above in paragraphs 66 - 83, the animal test data in the prior art Nakagawa Declaration would have suggested to a person of ordinary skill to add one methylene, so as to go from a “propoxy” to a “butoxy” linker.

158. The prior art 1987 Wise Poster also makes the same suggestion—namely, adding one methylene, so as to go from a “propoxy” to a “butoxy” linker.

159. Parke-Davis was studying the antischizophrenic potential of heterocyclic compounds called coumarins, while Otsuka was studying the antischizophrenic potential of heterocyclic compounds called carbostyrils.

160. The only structural difference between a carbostyryl and a coumarin is that the NH at the bottom of the carbostyryl group is replaced by an oxygen atom. Carbostyrils and coumarins are very close structural analogs of each other. Otsuka has previously submitted expert testimony to the PTO in connection with an interference proceeding involving the ‘416 patent wherein it affirmatively represented that coumarin is very close structurally to carbostyryl. This is reinforced by an internal Otsuka memorandum finding the Parke-Davis coumarins to be functionally and structurally similar to OPC-4392.

161. At the November 1987 annual meeting of the Society of Neurosciences in Louisiana, Dr. Wise and others from Parke-Davis displayed and distributed copies of a poster (the "1987 Wise Poster") reporting animal test results on coumarins. In head-to-head comparisons between a coumarin with a propoxy linker and one with a butoxy linker, the butoxy compound did better in two animal tests that are indicative of antischizophrenic potential in humans.

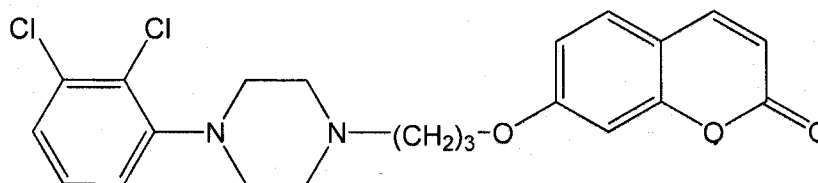
162. Because of the close structural similarity of coumarins to carbostyrils, and the prior-art documented similarity in function, these publicly disclosed results of animal tests on coumarins would have led a person of ordinary skill in the art to expect improvement in going from a propoxy to a butoxy linker in carbostyrils. The person of ordinary skill would have given extra weight to the change from propoxy to butoxy because the prior art contained more than one suggestion to do so.

163. As discussed above, a skilled person would have thought of chlorine as a substituent candidate on the phenyl ring. Chlorine is about the same size as methyl and would, therefore, not have been seen as a big structural change. Further, chlorine would have been selected because it already was known as an electron-withdrawing substituent that provided good activity when added to the phenyl ring.

164. The prior art 1987 Wise poster contains a head-to-head comparison between a propoxy coumarin with a *chlorine* substituted at the 3 position and a propoxy coumarin with a *methyl* substituted at the 3 position. In each of three different animal tests for the suppression of dopamine activity, which is an indicator of antischizophrenic potential, the chlorine was more potent than the methyl. That would have been another strong suggestion to substitute chlorine for methyl in OPC-4392 in order to improve its anti-schizophrenic potency.

165. The teachings of the Wise Poster are reinforced by U.S. Patent No. 4,701, 456, filed on June 18, 1985 and issued on October 20, 1987. The '456 patent discloses coumarin compounds useful as antipsychotic agents. Example 2 of the '456 patent is the coumarin analog of OPC-4392. Example 3 contains the 2,3 dichloro coumarin analog of OPC-4392.

7-{3-[4-(2,3-dichlorophenyl)-1-piperazinyl]propoxy}-2H-1-benzopyran-2-one
(“2,3-dichloro propoxy coumarin”), which has the following structural formula:



166. OPC-4392 was a double-bonded carbostyryl. OPC-4139 was a single-bonded carbostyryl. All nine of the compounds in the prior art Nakagawa Declaration's report of the mouse jumping test were single-bonded carbostyryls. The compounds of the Wise Poster and the '456 patent were analogs of the double-bonded carbostyryl. The skilled person would not have picked between these two alternatives, and instead have made both versions of each compound. This was, in fact, the very approach taken by Otsuka for many of the compounds exemplified in the Banno '416 patent where 251 pairs of single- and double-bonded carbostyryl compounds are disclosed. The Banno '416 patent is prior art to the '528 patent and was previously identified by Otsuka in the FDA Orange Book as covering aripiprazole. OPC-4392 and OPC-4139 fall within the scope of its claims. OPC-4139 even appears again in the Nakagawa Declaration.

167. In view of the foregoing, the skilled person would have gone forward to develop a group of compounds that included (1) changing from a propoxy to a butoxy linker, (2) substituting chlorine for methyl on the phenyl ring, and (3) using single bonds and double bonds in the carbostyryl as alternatives. This group would have included aripiprazole. Also, it is a rational scheme. That is demonstrated by Oshiro's 1998 paper that shows 7 of 8 possible 2,3-

chloro-methyl combinations were made by Otsuka. It was the only set of combinations that was so thoroughly explored.

168. The only differences between OPC-4392 and aripiprazole are that: (1) aripiprazole has a butoxy ($\text{O}(\text{CH}_2)_4$), rather than a propoxy ($\text{O}(\text{CH}_2)_3$), linker; (2) aripiprazole has chlorines (Cl), rather than methyls (CH_3), at positions 2 and 3 on the phenyl ring; and (3) aripiprazole has a single bond (single line in upper left), rather than a double bond (double line in upper left), in the carbostyryl group. As explained above, those are the very changes suggested by the prior art. Accordingly, it would have been obvious to make aripiprazole and use it to treat schizophrenia with a reasonable expectation of success.

169. Otsuka contends that a person of ordinary skill in the art would have considered 5-linked compounds. But a 5-isomer analog of OPC-4392 (in a single bonded version) had already been made before, along with a number of other 5-isomer propoxy compounds, and the 7-linked OPC-4392 was the compound selected for clinical trials. Assuming *arguendo* that a person of ordinary skill in the art would have considered 5-linked compounds, based on the teachings of the prior art the person of ordinary skill would have had a preference for substituting it with 2,3 methyls and chloros, but would not leave them unsubstituted or use ethoxy substitutions. The person of ordinary skill also would have extended the inference of more potency in the butoxy in 7-linked compounds to 5-linked compounds and made butoxy analogs of those compounds. But given the greater amount of data for 7-position butoxy compounds the person of ordinary skill in the art still would have had a preference for 7-position compounds over 5-position compounds in her development efforts.

g. Secondary Considerations Do Not Support a Finding of Non-Obviousness

i. Commercial Success

170. Otsuka cannot rely on evidence of the alleged commercial success of aripiprazole as tending to show the nonobviousness of the '528 patent. The relevance of commercial success to obviousness relies on the inference that others must have tried and failed. That inference cannot be drawn here. Competition in the marketplace by others was blocked by Otsuka's patent position with respect to carbostyryl derivatives. Thus, the explanation for why others did not develop or pursue the aripiprazole option is not the alleged nonobviousness of aripiprazole, but rather that Otsuka had already blocked out all others from pursuing it. Accordingly, there is no logical connection between nonobviousness and alleged commercial success in this case.

171. While Otsuka's extensive patenting of carbostyryl derivatives as potential antischizophrenia agents prevented others from exploiting these compounds, other researchers, before the development of aripiprazole, were able to develop other compounds as atypical antischizophrenic drugs and obtain FDA approval for marketing in the U.S. well before aripiprazole was approved by the FDA in November 2002. Several of these antischizophrenic drugs, including risperidone, olanzapine and quetiapine consistently outsell aripiprazole in the U.S. market for atypical antischizophrenic drugs. The evidence of commercial success of aripiprazole, even if relevant, does not weigh in Otsuka's favor on the nonobviousness of the asserted claims of the '528 patent.

172. Further, there is a lack of nexus between the claimed commercial success of aripiprazole and the '528 patent claims at issue. Claims 17 and 23 are directed to the use of aripiprazole for the treatment of schizophrenia. Since receiving FDA approval in November 2002 for the use of aripiprazole in the treatment of schizophrenia, Otsuka has filed a number of Supplemental New Drug Applications with the FDA seeking approval for aripiprazole in the treatment of conditions other than schizophrenia. As a result of these efforts, Otsuka has

obtained, for example, FDA approval to market aripiprazole for the treatment of Bipolar I Disorder and Major Depressive Disorder.

173. The general patient population in the U.S. affected by schizophrenia is estimated at approximately 1%. Excluding “typical” antischizophrenic drugs, aripiprazole was the sixth “atypical” antischizophrenic drug to obtain FDA approval for use in the treatment of schizophrenia. Currently, there are seven approved “atypical” antischizophrenic drugs for the treatment of schizophrenia in the U.S. Two of these “atypical” antischizophrenic drugs, clozapine and risperidone, have gone off-patent and are available in generic form.

174. With each newly approved indication of use obtained from the FDA, the general population for which aripiprazole may legally be prescribed has jumped markedly beyond the 1% affected by schizophrenia.

175. Otsuka is unable to distinguish the total sales, new prescription growth, and repeat prescription growth of aripiprazole attributable solely to its use in the treatment of schizophrenia.

176. Since obtaining initial approval for the treatment of schizophrenia, and even after winning approval for additional indications of use other than in the treatment of schizophrenia from the FDA, aripiprazole has never been able to rise higher than third in overall sales behind quetiapine and risperidone.

177. Otsuka’s alleged commercial success in 2002 – 2005 is tainted by its promotion and sale of aripiprazole for off-label uses. In this misconduct, it is joined by its co-promotional partner in the U.S., Bristol-Myers Squibb (“BMS”). Specifically, Otsuka paid over \$4,000,000 to settle allegations that it actively engaged in the promotion and sale of aripiprazole for pediatric use and to treat dementia-related psychosis—at the time both off-label uses of aripiprazole. In

addition, Otsuka entered into a Corporate Integrity Agreement with the Office of the Inspector General of the Department of Health and Human Services.

178. In turn, BMS paid a total of \$515,000,000 to settle charges that included the off-label promotion and sale of aripiprazole for pediatric use and to treat dementia-related psychosis during the 2002 – 2005 time frame. Out of this settlement, \$25,000,000 represented the disgorgement of profits earned from the off-label promotion of aripiprazole. BMS also entered into a Corporate Integrity Agreement with the Office of the Inspector General of the Department of Health and Human Services.

179. Otsuka and BMS do not know what percentage of sales in the 2002 – 2005 time frame are attributable to the off-label promotion of aripiprazole.

180. Factors other than the alleged benefits of claims 12, 17, and 23 of the '528 patent are responsible for the claimed commercial success of aripiprazole. Such factors include the promotion and marketing efforts, sales budget, and sales force commitments employed by Otsuka and BMS to promote aripiprazole including, for a time, the off-label promotion of aripiprazole. Among its competitors, Otsuka and BMS have spent significantly more money in the promotion and sale of aripiprazole including direct-to-consumer print and TV advertising with respect to their use in the treatment of Bipolar I Mania and Major Depressive Disorder. In 2009 alone, Otsuka and its co-promotional partner, BMS, spent more than \$202,000,000 on ads that resulted in a 30% increase in sales.

ii. Long-Felt and Unsolved Need

181. Otsuka argues that the development of aripiprazole solved a long-felt need for a safe and effective antipsychotic for the treatment of schizophrenia with reduced side effects. The evidence does not show that aripiprazole solved this long-felt need and, indeed, this problem

remains unsolved to date. The ultimate long-felt and unsolved need is for the development of a cure for schizophrenia that does not involve a trade-off between efficacy and side effects. The alleged facts relied upon by Otsuka for establishing its version of the long-felt but unsolved need do not support the inference upon which this secondary consideration of non-obviousness is based and does not overcome Defendants' strong showing of obviousness. The relevance of long-felt need to obviousness relies on the inference that others must have tried and failed, i.e. they tried and were unsuccessful in solving the long-felt need of developing a safe and effective antipsychotic for the treatment of schizophrenia with reduced side effects. As discussed with respect to commercial success, the inference cannot logically be drawn here. In the first instance, the development of aripiprazole or carbostyryl compounds by others in seeking to address the long-felt need would have been discouraged by Otsuka's blocking patent position. Thus, the explanation for why others did not develop the aripiprazole option or conduct research into the potential use of carbostyryl compounds is not the alleged nonobviousness of aripiprazole, but rather that Otsuka had already blocked out all others from pursuing this route. Accordingly, there is no logical connection between nonobviousness and long-felt and unsolved need in this case.

182. To the extent that aripiprazole addressed what Otsuka claims is the long-felt and unsolved need for a safe and effective antipsychotic for the treatment of schizophrenia with reduced side effects, it is neither unique nor the first compound in the class known as atypical antipsychotics. While Otsuka's extensive patenting of carbostyryl derivatives as potential antipsychotics prevented others from exploiting these compounds, other researchers were able to develop other compounds, before the development of aripiprazole, as antischizophrenic drugs to address the long-felt and unsolved need and obtained FDA approval for marketing in the U.S.

By October 31, 1988, these other atypical antischizophrenic drugs had addressed the long-felt need for a safe and effective antipsychotic for the treatment of schizophrenia with reduced side effects. Several of these antischizophrenic drugs consistently outsell aripiprazole in the market.

183. While Otsuka was conducting research into carbostyrils and pursuing patenting of carbostyryl derivatives in the 1980s (including the '932 patent, the '416 patent, and the '840 patent), other pharmaceutical companies were pursuing their own lines of research into antipsychotic drugs for the treatment of schizophrenia and were successful in developing, testing, patenting, and gaining FDA approval to market well before aripiprazole

184. In late 1993, risperidone (marketed by Janssen as Risperdal[®]) became the second atypical antipsychotic drug, after clozapine, to receive FDA approval for the treatment of schizophrenia. U.S. Patent No. 4,804,663 for risperidone has a filing date of March 3, 1985—more than three years before the filing of Otsuka's Japanese priority patent application on October 31, 1988. The development of risperidone addressed the long-felt need for a safe and effective antipsychotic for the treatment of schizophrenia with reduced side effects. *Janssen Pharmaceuticals N.V. v. Mylan Pharmaceuticals, Inc.*, 456 F.Supp.2d 644, 670 (DNJ 2006).

185. In September 1996, olanzapine (marketed by Eli Lilly as Zyprexa[®]) became the third atypical antipsychotic drug to receive FDA approval for the treatment of schizophrenia. U.S. Patent No. 5,229,382 for olanzapine was filed on May 22, 1992, as a continuation of an earlier abandoned patent application filed on April 23, 1991. Olanzapine was first synthesized in 1982 and, by 1988, was in clinical trials to test its efficacy in actual schizophrenic patients. *Eli Lilly and co. v. Zenith Goldline Pharmaceuticals, Inc.* 364 F.Supp.2d 820, 834-35 (S.D. Ind. 2005). Olanzapine represents another compound that successfully addressed the long-felt need

for a safe and effective atypical antipsychotic for the treatment of schizophrenia with reduced side effects.

186. In 1997, quetiapine (marketed by AstraZeneca as Seroquel®) was the next atypical antipsychotic drug to receive FDA approval for the treatment of schizophrenia. U.S. Patent No. 4,879,288 for quetiapine was filed on March 27, 1987, and claims a foreign priority date of March 27, 1986 – more than 2 ½ years before the filing date of Otsuka's Japanese priority patent application. Like risperidone and olanzapine, quetiapine represents yet another compound that successfully addressed the long-felt need for a safe and effective atypical antipsychotic for the treatment of schizophrenia with reduced side effects.

187. Ziprasidone (marketed by Pfizer as Geodon®) next received FDA approval in February 2001. U.S. Patent No. 4,831,031 for ziprasidone was filed on January 22, 1988 – ten months before the filing date of Otsuka's Japanese priority patent application. This was the fifth FDA-approved atypical antipsychotic compound that successfully addressed the long-felt need for a safe and effective atypical antipsychotic for the treatment of schizophrenia with reduced side effects.

188. In November 2002, aripiprazole (Abilify®) became the sixth “atypical” antipsychotic to receive FDA approval for use in the treatment of schizophrenia. The '528 patent was filed in the U.S. on October 20, 1989, claiming a foreign priority filing date of October 31, 1988.

189. In 2006, paliperidone (marketed by Ortho McNeil/Janssen as Invega®) received FDA approval for use in the treatment of schizophrenia. U.S. Patent No. 5,158,952 (the “'952 patent”) for paliperidone was filed on October 17, 1989, as a continuation-in-part of an earlier abandoned patent application filed on November 7, 1988 – just 7 days after the filing of Otsuka's

Japanese priority patent application. Paliperidone is another example of an atypical antischizophrenic compound that successfully addressed the long-felt and unsolved need for a safe and effective antipsychotic for the treatment of schizophrenia with reduced side effects.

190. At present, there are seven "atypical" antischizophrenic drugs approved in the U.S. for the treatment of schizophrenia. The majority of these atypical antischizophrenic drugs were developed and the subject of U.S. patent applications before the October 31, 1988 foreign priority date for aripiprazole. None of the atypical antipsychotics cure schizophrenia and none of them are without side effects. All of these are recognized, as compared to typical antipsychotics, as being useful in the treatment of schizophrenia with reduced side effects. The totality of the circumstances shows that numerous avenues for addressing the long-felt need for a safe and effective antipsychotic for the treatment of schizophrenia with reduced side effects were developed by others before October 31, 1988.

191. There was no long-felt but unsolved need for aripiprazole since a number of competitive atypical antipsychotic compounds were developed, patented, and approved for use in the treatment of schizophrenia with reduced side effects before the development, patenting, and approval of aripiprazole. Moreover, the long-felt need has yet to be solved as there remains no known cure for schizophrenia and there is no current drug treatment for schizophrenia that does not involve unwanted side effects.

iii. Unexpected Results

192. Validity is also not supported by unexpected results because improvement was to be expected from chlorine substitution and a change from a propoxy to butoxy linker. As explained above, aripiprazole is among the group of compounds that the person of ordinary skill would have selected as candidates for a new antischizophrenic drug based on prior art suggested

modifications of carbostyryl derivatives. Members of that group of compounds would have been expected to have improved potency because that was what the prior art suggested would happen in switching from a propoxy linker to a butoxy linker and in switching to a chlorine substituent on the phenyl ring. Thus, even if aripiprazole were to possess such an improved potency, that would not qualify as evidence of “unexpected superiority,” because any “unexpected superiority” would have been expected, not unexpected.

193. Further, the 1998 Oshiro article reports animal testing on aripiprazole and several other compounds that are modifications from OPC-4392 along the lines set forth above (*i.e.*, butoxy compounds with chlorine substitutions and single or double bonds). The animal test results in the 1998 Oshiro article reveal that aripiprazole was not the best in several of these tests.

194. In addition to the lack of unexpectedly superior values, the apomorphine-induced stereotypy test used in the Hirose Declaration is considered to be more indicative of side effects more than the positive symptom potency of antischizophrenic compounds. Therefore, one of skill in the art would not have relied on results from the stereotypy test to show unexpected superiority of antischizophrenic agents.

195. During the reexamination of the '528 patent, the Hirose Declaration was submitted to the PTO, purporting to compare four compounds in the '528 patent, including aripiprazole, with what it states are structurally similar compounds. Eight compounds were tested in Otsuka's attempt to demonstrate unexpected results. The eight compounds tested for the Hirose Declaration did not include the unsubstituted butoxy.

196. One of the test comparisons used the anti-apomorphine stereotypy test (“stereotypy test”). Apomorphine produces stereotypy by stimulating dopamine receptors in the striatum.

197. Insofar as a compound inhibits apomorphine-induced stereotypy it is reasonable to suggest that the compound has an anti-dopaminergic action. However, compounds appear to require anti-dopaminergic action in the nucleus accumbens to be effective antischizophrenics. Further, it appears that an anti-dopaminergic action in the striatum is indicative of EPS, one of the most troublesome side effects of antischizophrenic medication.

198. By the late 1980s and certainly by September 14, 2005, when the Hirose Declaration was submitted to the PTO, it was known and accepted that animal tests that tested for antagonism of dopamine receptors in the nucleus accumbens of the brain were indicative of antipsychotic potential and animal tested that tested for antagonism of dopamine receptors in the nigrostriatal region (striatum) of the brain were indicative of unwanted EPS.

199. Consequently, other types of tests have replaced the stereotypy test as a model for potential antischizophrenic activity. Moreover, at least by 2005, the stereotypy test was used in many studies to explicitly assess a compound's liability for causing unwanted EPS.

200. In addition, several effective and well-known antipsychotic drugs only weakly inhibit apomorphine-induced stereotypy—*e.g.*, clozapine, sertindole, and ziprasidone have little to no effect on stereotypy.

201. Further, the stereotypy test produces false positives. For example, fenfluramine and metoclopramide, two compounds devoid of antipsychotic potency, inhibit apomorphine-induced stereotypy.

202. Thus, whether a compound strongly inhibits stereotypy says little about its antipsychotic potency. Stereotypy data by itself, therefore, cannot be used to assess the relative antipsychotic potency of a compound, *i.e.*, whether a compound is a superior agent for treating schizophrenia as compared to other compounds.

203. As such, the data provided in the Hirose Declaration do not establish that the compounds claimed in the '528 patent are superior agents for treating schizophrenia with less side effects. Rather, they establish that the compounds of the invention have a high potential liability for causing EPS side effects.

204. A goal in developing antipsychotic drugs is to optimize the balance between a drug's desired activity and its undesired side effects. Thus, any comparison of the apomorphine-induced stereotypy test with other side effect tests (*e.g.*, epinephrine lethality or catalepsy) to form a ratio between their ED₅₀ values does not constitute a therapeutic index, in that the index would be comparing side effects to side effects, and not side effects to desired activity. Therefore, one cannot use a ratio of epinephrine lethality data and stereotypy data to indicate that a compound is a superior agent for treating schizophrenia as compared to other compounds.

205. Even if the data provided in the Hirose Declaration could show that the compounds in the '528 patent are superior agents for treating schizophrenia, the Hirose Declaration nevertheless fails to show unexpected results because it does not compare aripiprazole directly to the unsubstituted butoxy.

206. The data in the Hirose Declaration cannot be reasonably relied on because the experimental protocol is flawed.

207. The protocol in the Hirose Declaration employs a subjective scale for scoring stereotyped movements in mice. The scale only has four scores and the two raters were required to make qualitative, personal judgments about which of the four scores best describes a mouse's behavior at a certain time.

208. Because the stereotypy scale is subjective, variation in scoring often arises when more than one scorer is used, since the two scorers may apply the scoring scale differently.

When making difficult and subjective judgment calls, a consciously or unconsciously biased rater may give the “benefit of the doubt” to the claimed compounds.

209. Therefore, because the two scorers did not standardize their interpretation of the stereotypy scoring scale or that a high correlation was achieved between the scoring, observed differences could have been due to the compounds or they could have been due to the different raters. This creates a confound in the data and thus meaningful comparisons cannot be drawn from it. Furthermore, the test protocol given to the Examiner mentions only one observer so the Examiner could not have been aware of this.

210. The scorers of stereotypy movements also were not blind to which compounds they were testing—*i.e.*, the scorers knew which mice were treated with the prior art compounds and which mice were treated with the claimed compounds.

211. The Examiner was not informed of this since the test protocol given to the Examiner indicates that the scoring was blind to the treatment received by the mice.

212. True blind scoring is used to prevent test results from being influenced by observer bias. If truly blind, the scorer will not know whether a mouse has been given the control or a test compound—and, if a test compound has been given, will not know which test compound has been given.

213. This is important because, as discussed above, the stereotypy rating scale demands that the observer not only judge whether *any* stereotypy has occurred, but also assess the *extent* of the stereotypy. When making these difficult judgments, a non-blinded observer may—consciously or unconsciously—give better scores to the claimed compounds because they are allegedly more active, particularly when the purpose of the study is not to evaluate the relative potencies but to prove that one set of compounds was more potent than another. Since the study

was not truly blind, meaningful comparisons cannot be drawn from the data presented in the Hirose declaration. Of course, the Examiner was unaware that the actual testing conducted by Otsuka and reported in the Hirose Declaration deviated significantly from the test protocol given to the Examiner.

214. Therefore, even if the stereotypy test were incorrectly accepted as a measure of antischizophrenic effectiveness, the methodology employed was fundamentally flawed by a high likelihood of confound/bias such that the results cannot be meaningfully compared and thus do not demonstrate “unexpected superiority.”

215. Thus, there is no evidence that aripiprazole possesses unexpected superiority over the closest prior art compounds, including the unsubstituted butoxy.

iv. Copying

216. The fact that Defendants have filed Abbreviated New Drug Applications (“ANDAs”) with the FDA seeking approval to sell aripiprazole before the expiration of the ’528 patent—*i.e.*, copying—is not relevant to the issue of the non-obviousness of the ’528 patent because Defendants’ actions are consistent with the underlying goal of the Hatch-Waxman Act to bring lower-cost generic drugs to market as quickly as possible. In the ANDA context where Defendants are required to show bioequivalency to obtain FDA approval, Otsuka’s evidence of copying is not compelling evidence of nonobviousness. In addition, any evidence of copying of aripiprazole in the research and patenting efforts of certain of the Defendants is protected by the safe harbor provision of 35 U.S.C. § 271.

v. Industry Acclaim

217. There is a lack of nexus between claims 12, 17, and 23 of the ’528 patent and Otsuka’s alleged evidence of industry acclaim. Other atypical antipsychotics, including both

risperidone and olanzapine, pre-dating the October 31, 1988 foreign priority date for aripiprazole, have also received similar industry acclaim as that received for aripiprazole suggesting that all atypical antipsychotics that have been approved by the FDA have received the same or similar industry acclaim.

218. Despite its side effects, clozapine remains the most effective “atypical” antipsychotic for the treatment of schizophrenia.

219. Literature published since the introduction of aripiprazole involving a comparison of several “atypical” antischizophrenic drugs confirm that aripiprazole is no better than, and in some cases worse than, its competitors in terms of efficacy, side-effect profile, and mean-time before discontinuation of use. Further, any industry acclaim which have may be attributed to aripiprazole is mitigated by the fact that other antischizophrenics, which came onto the market before aripiprazole, have been similarly honored. Additionally, to the extent that aripiprazole has received acclaim it was for Otsuka’s entire carbostyryl development program, much of which includes the development of prior art compounds such as OPC 4392 and OPC 4139, as well as the compounds of its own prior art ’416 patent. The routine optimization necessary to reach aripiprazole from this substantial body of prior art does not in and of itself account for the industry acclaim, and cannot be separated from the earlier work that already was in the prior art.

4. Claims 12, 17, and 23 of the ’528 Patent Are Invalid Because the ’528 Patent Lacks Support for Antischizophrenic Effectiveness

220. Asserted claim 17 of the ’528 patent depends from claim 16 that recites, *inter alia*, a “composition for treating schizophrenia.” Asserted claim 23 recites, *inter alia*, a “method of treating schizophrenia.” Asserted claim 12 recites the chemical name for aripiprazole and does not mention schizophrenia; however, treating schizophrenia is the only practical use for aripiprazole mentioned in the specification of the ’528 patent.

221. The '528 patent reports results of only two types of tests, the anti-epinephrine lethal activity test and the anti-apomorphine stereotypy test.

222. The anti-epinephrine lethal activity test has some correlation to a potential side effect—namely, orthostatic hypotension. The test is not predictive of antischizophrenic activity and Otsuka does not so contend.

223. With respect to the anti-apomorphine stereotypy test, the written description in the '528 patent does not state that this test is predictive of antischizophrenic activity.

224. In his declaration filed during original prosecution of the '528 patent, Dr. Oshiro, a named inventor on the '528 patent, represented to the Examiner that success in the anti-apomorphine stereotypy test is an “indication for showing the strength of major activity for blocking neurotransmission of dopaminergic receptor.”

225. Besides the aforementioned, the PTO was provided with no other explanation from Otsuka of the meaning to be derived from the results of the anti-apomorphine stereotypy test.

226. The anti-apomorphine stereotypy test results in the '528 patent are not adequate to establish antischizophrenic effectiveness.

227. It was known that the anti-apomorphine stereotypy test was an indicator of unwanted extrapyramidal side effects (“EPS”) as opposed to being an indicator of antischizophrenic effectiveness.

228. The anti-apomorphine stereotypy test is not sufficient, on its own or in combination with the anti-epinephrine lethality test, to have led a person of ordinary skill in the art to believe that the compounds claimed in the '528 patent would have been effective to treat schizophrenia.

F. The '528 Patent Is Unenforceable for Inequitable Conduct

1. Withholding the Nakagawa Declaration and Parke-Davis Work from United States Patent and Trademark Office

229. Otsuka, through certain employees and attorneys, convinced the examiners during the original prosecution and the reexamination to allow the '528 patent solely on the basis that the switch from a propoxy linker to a butoxy linker resulted in an "unexpected" improvement.

230. While Otsuka's employees and attorneys were telling the PTO that the switch from a propoxy to a butoxy linker yielded "unexpected" improvement, Otsuka's employees and attorneys had knowledge of prior art that suggested that such a switch can be expected to bring improvement.

231. Those working for and on behalf of Otsuka with a duty to disclose material information never told the examiners during either the original prosecution or the reexamination of the '528 patent about the prior art Nakagawa Declaration and its data suggesting that improvement would be expected from changing from a propoxy linker to a butoxy linker in a carbostyryl.

232. Otsuka's employees and attorneys knew all about the prior art Nakagawa Declaration. First, the Nakagawa Declaration was presented on Otsuka's behalf to the examiner of the Banno '416 patent by the very same law firm that represented Otsuka during the prosecution and reexamination of the '528 patent. Second, Dr. Oshiro, an Otsuka employee, is a named inventor on both the '416 and '528 patents.

233. Individuals acting on behalf of or for Otsuka during the prosecution of the Banno '416 patent who owed a duty to disclose material information to the Examiner during the original prosecution and reexamination of the '528 patent include: Yasuo Oshiro (a co-inventor on both the Banno '416 and '528 patents and member of Otsuka's IP Department), additional members of Otsuka's IP Department (including Katuyoshi Yamamoto), and prosecuting attorneys from the Finnegan firm (including Arthur S. Garrett).

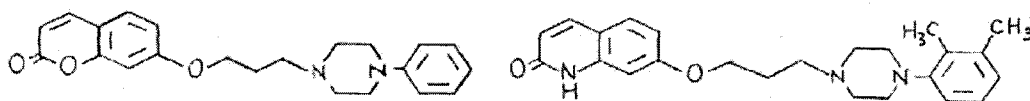
234. During reexamination of the '528 patent, Otsuka made representations that could not have been made if the reexamination examiner had been shown the prior art Nakagawa Declaration. For example, Otsuka repeatedly and misleadingly told the reexamination examiner that there was "no evidence" that the unsubstituted butoxy carbostyryl compound may be useful in treating schizophrenia. This statement is refuted by the prior art Nakagawa Declaration's report that the very same unsubstituted butoxy compound was "excellent" in the mouse jumping test—*i.e.*, the very test that Otsuka told a different examiner in another application (for the '932 patent) was a "test method for determining whether a compound will have antischizophrenic activity."

235. Otsuka also kept from the examiners in both the original prosecution and reexamination of the '528 patent the Parke-Davis work on coumarins which also suggests the switch from a propoxy to a butoxy linker to improve antipsychotic activity.

236. An internal Otsuka memo dated September 5, 1988 (just before the October 31, 1988, filing date of the Japanese priority application for aripiprazole), demonstrates that Otsuka, including one of the inventors on the '528 patent, Dr. Oshiro, had actual knowledge of the Parke-Davis work and appreciated its similarity to carbostyryls. The text of this memo from S. Haruki to Manager Kabe, with a copy to the co-inventor Dr. Oshiro, reads as follows:

Greetings

We have a report regarding PD-116795 (Park [sic] Davis, a subsidiary of Warner-Lambert), which has a structure similar to OPC-4392, and although you already know this as per your previous guidance, I am informing you of it. As shown in the following, PD-116795 is very similar in structure to OPC-4392, having a coumarin skeleton in which an oxygen atom is substituted for a nitrogen atom in the carbostyryl [sic], which is the parent core of OPC-4392.



PD-116795

OPC-4392

Although as of now we have not obtained any detailed reports since it was reported at the Society for Neuroscience (Louisiana, U.S.) last year, the profile, such as its having a dopamine autoreceptor agpnist [sic] action, is also like that of OPC-4392.

Sincerely yours,

CC: Director Ohara, General Researcher Oshiro, Researcher Kikuchi

237. There are only minor differences in structure between OPC-4392 and aripiprazole. Moreover, Otsuka, during an interference proceeding in the PTO involving the '416 patent, provided expert testimony that coumarin (the subject of Parke-Davis's publicly disclosed antipsychotic research) is very close in structure to carbostyryl.

238. OPC-4392 was the historical basis, in fact, for aripiprazole as confirmed by several publications by Otsuka researchers.

239. Thus, what the Haruki memo is telling the recipients, including the co-inventor Dr. Oshiro, is that Parke-Davis' work on coumarins, specifically PD-116795, is closely related to Otsuka's work on OPC-4392 that led to aripiprazole. The Haruki memo included a copy of a published Japanese patent application further describing the Parke-Davis work on coumarins as antipsychotics. That Japanese patent application was a foreign counterpart of the '456 patent. Neither the '456 patent nor its Japanese counterpart were ever disclosed to the USPTO. Not even in the reexamination.

240. The second paragraph's reference to the report published at the 1987 meeting of "The Neuroscience Society (Louisiana, USA)" establishes that Otsuka knew of the prior art 1987 Wise poster.

241. At no time was the reexamination examiner told by Otsuka or its representatives about the prior art 1987 Wise poster, even though it suggests that going from a propoxy linker to a butoxy linker would lead to improvement.

**2. Dr. Hirose's Fraudulent Declaration Submitted During the
Reexamination of the '528 Patent**

242. In his Declaration, Dr. Hirose identified four compounds covered by the claims of the '528 patent, and stated: "In my opinion, these four compounds are representative of the carbostyryl compounds claimed in the above-identified U.S. Patent No. 5,006,528." Dr. Hirose also identified four prior art compounds, and stated: "In my opinion, the compounds of the applied references, which are the most structurally similar with carbostyryl derivatives claimed in the above-identified U.S. Patent No. 5,006,528, are those compounds that have a propoxy bridging group, rather than the requisite butoxy bridging group of the claimed compounds."

243. The statements by Dr. Hirose in the preceding paragraph are untrue.

244. Dr. Hirose testified that he could not identify similarities or differences between the compounds he tested because he did not have knowledge of organic chemistry. Dr. Hirose testified that lawyers wrote the Declaration for him, and that he informed attorneys working with him that he did not have a strong background in organic chemistry.

245. Dr. Oshiro, an organic chemist, testified that the unsubstituted butoxy compound could be recognized as structurally closer than the homologs identified by Dr. Hirose in the Hirose Declaration.

246. Dr. Hirose also stated in his Declaration that "[a]nti-apomorphine activity is a strong indicator of a compound's ability to block neurotransmission of dopaminergic D2-receptors, i.e., its antipsychotic potency." Dr. Hirose relied on the differences in anti-

apomorphine activity to contend that the claimed compounds of the '528 patent were unexpectedly superior to the prior art compounds.

247. Dr. Hirose's statement was misleading because it was known that the anti-apomorphine stereotypy test was insufficient to establish antipsychotic activity.

248. Dr. Hirose's declaration is also false and misleading because the data are confounded and biased and cannot be meaningfully compared due to failure to properly blind the study and standardize scoring by different observers.

249. The Hirose Declaration includes a protocol which informed the examiner that only one observer was used to perform the stereotypy test. This was not the actual case. Two observers were used by Otsuka. Because the protocol employs a subjective scoring scale and scoring varies between different observers, absent controls, results are generally considered unreliable such that meaningful comparisons from the data cannot be drawn. No such controls were used and the Examiner was not informed that, contrary to the protocol, more than one observer was used.

250. The protocol for the tests in the Hirose Declaration also informed the examiner that the tests were blinded. However, the observers were not blind to the compounds which were being tested and also had knowledge of the purpose of the test. Thus, a high risk of bias was introduced into the study which would not allow meaningful comparisons of the data obtained. The examiner was not informed, contrary to the protocol, that the observers were not blind to the compounds tested.

251. The Hirose Declaration also states that "anti-epinephrine activity is a significant indication for showing side effects associated with antipsychotic medication." This statement is false and misleading because the anti-epinephrine test is a test only for orthostatic hypotension

and does not take into account other serious side effects, including EPS, which is generally considered one of the most serious side effects of antipsychotic medications. Rather the apomorphine stereotypy test, which was presented as indicative of antipsychotic activity, is actually more indicative of EPS and was not so disclosed to the examiner.

252. In the Hirose Declaration, Dr. Hirose concluded that the “greater potency exhibited by the compounds claimed in the above-identified U.S. Patent No. 5,006,528 could not be predicted by the teachings of the prior art.”

253. Because Dr. Hirose, given his stated lack of knowledge of organic chemistry, could not identify the similarities or differences between the claimed compounds and the prior art compounds, Dr. Hirose was incapable of representing to the examiner that the potency of the claimed compounds could not be predicted based on the known prior art compounds.

254. Each of the foregoing fraudulent statements were material to the patentability of the '528 patent as the examiner relied on Dr. Hirose's Declaration for purposes of overcoming the examiner's rejections and allowing the claims. Further, the statements were made with the intent to deceive the examiner as to the differences between the compounds of the prior art and the compounds of the '528 patent.

(2) Defendant intends to prove the following contested facts with regard to damages. (This statement must include the factual basis for each defense against plaintiff's claims for damages).

This is an ANDA litigation and therefore damages are not an issue. Defendants reserve the right to seek their costs and attorneys fees associated with their respective exceptional case claims pursuant to 35 U.S.C. Section 285. In the event Plaintiff seeks the recovery of damages or other monetary relief in connection with any commercial sale of aripiprazole by one or more

of the Defendants, Defendants reserve the right to put on a rebuttal case with respect to damage or other monetary relief.

Defendants intend to contest Plaintiff's entitlement to temporary, preliminary and/or permanent injunctive relief in this action including all grounds upon which Plaintiff's will rely in seeking injunctive relief. Defendants note that additional discovery may be warranted with respect to any request by Plaintiff for injunctive relief. In the event that Defendants prevail on the merits of this action at trial, Defendants will oppose any request by Plaintiff for a stay pending appeal.

6. PLAINTIFF'S WITNESSES (Aside from those called for impeachment purposes, only those witnesses whose names and addresses are listed below will be permitted to testify at trial).

A. On Liability, Plaintiff Intends To Call The Following Witnesses Who Will Testify In Accordance With The Following Summaries:

Defendants have stipulated to infringement of the asserted claims 12, 17 and 23 of the '528 patent and therefore Otsuka need not prove infringement at trial. Moreover, as the '528 patent is presumed valid (35 U.S.C § 282), Otsuka has no burden of proof regarding Defendants' affirmative defenses and counterclaims that the asserted claims of the '528 patent are invalid or unenforceable. Defendants alone must prove these affirmative defenses and counterclaims by clear and convincing evidence. Without assuming any burden of proof, Otsuka expects that it may call the following fact witnesses in person in response to Defendants' affirmative defenses and counterclaims of invalidity and/or unenforceability. To the extent permitted by Judge Cooper at trial, Otsuka reserves the right to amend and update this list to rebut any unanticipated evidence or argument Defendants may raise at trial and reserves the right to call any witness identified by Defendants.

Any amendment will be subject to a showing of manifest injustice.

1. Dr. Yasuo Oshiro

Dr. Oshiro was a research chemist at Otsuka, and is currently an advisor to Otsuka in Tokushima, Japan. Dr. Oshiro is the first named inventor of the '528 patent. Otsuka may call Dr. Oshiro to testify regarding his discovery of aripiprazole, the Oshiro declaration, and related technical aspects of the '528 patent.

2. Dr. Tsuyoshi Hirose

Dr. Hirose was a research chemist at Otsuka during the original prosecution and reexamination proceedings of the '528 patent. Dr. Hirose's declaration was submitted during the reexamination of the '528 patent. Otsuka may call Dr. Hirose to testify regarding aripiprazole's stereotypy and epinephrine lethality test results, the unexpected superiority of aripiprazole's test results over the prior art, the Hirose declaration, and related technical aspects of screening drugs for potential antipsychotic activity.

3. Charles Van Horn

Mr. Van Horn is an attorney who represented Otsuka in the reexamination of the '528 patent. Otsuka may call Mr. Van Horn to testify regarding non-privileged aspects of the reexamination of the '528 patent.

4. Mark Altmeyer

Mr. Altmeyer is President and Chief Executive Officer of Otsuka America Pharmaceutical Inc. Otsuka may call Mr. Altmeyer to testify concerning how the sales of Otsuka's Abilify[®] product would be impacted by a commercial launch of Defendants' generic products and the resulting irreparable harm to Otsuka. Defendants' discovery-related objections to Mr. Altmeyer were addressed by Judge Goodman during the June 1 Pretrial Conference and also during a June 7 teleconference. Judge Goodman ordered during the Pretrial Conference that

Otsuka provide Mr. Altmeyer for his deposition prior to June 15. Otsuka did so, and Defendants declined to proceed with his deposition.

In addition to the foregoing, Otsuka intends to introduce at trial deposition testimony of the witnesses identified in its deposition designations.

B. On Damages Plaintiff Intends To Call The Following Witnesses Who Will Testify In Accordance With The Following Summaries:

Otsuka is not seeking damages for the claims currently set for trial in this matter. Therefore, Otsuka does not intend to call witnesses who will testify regarding damages. Otsuka, however, reserves the right to seek damages should Defendants engage in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of Defendants' generic aripiprazole products described in Defendants' respective ANDAs before the expiration of the '528 patent. Otsuka further reserves the right to seek its costs and attorney fees associated with its exceptional case claim pursuant to 35 U.S.C. §§ 285 and 271(e)(4).

C. Defendants Object To The Following Witnesses For The Reasons Stated:

1. M. Altmeyer -- Defendants object to Mr. Altmeyer as a fact witness for Plaintiff under Fed. R. Evid. 401, 402, and 403. Any testimony provided by Mr. Altmeyer regarding how the sales of Otsuka's Abilify® may be impacted by a commercial launch of Defendants' generic products and any resulting harm is speculative and irrelevant to this case given the August 4th trial date.. Moreover, Defendants object to Mr. Altmeyer on the ground that Otsuka failed to timely identify this witness during fact discovery or in response to Defendants' various written discovery requests. Defendants further object to Mr. Altmeyer to the extent that his testimony constitutes expert opinions that have not be disclosed as required by the Federal Rules of Civil Procedure of the various Pretrial Scheduling Orders entered in this case.

7. **DEFENDANTS' WITNESSES (See instructions above).**

A. **On liability, defendants intend to call the following witnesses who will testify in accordance with the following summaries:**

On liability, Defendants have requested that Otsuka bring the following three named inventors on the '528 patent to trial: (1) Yasuo Oshiro; (2) Seiji Sato; and (3) Nobuyuki Kurahashi. All three named inventors are Japanese citizens. Defendants have also requested that Otsuka bring to trial the following fact witnesses with information relevant to the development of aripiprazole at Otsuka: (1) Tetsuro Kikuchi; and (2) Takashi Hiyama. Messrs. Kikuchi and Hiyama are Japanese citizens. Defendants have requested that Otsuka bring Shinichiro Haruki, another Japanese citizen, to trial to testify about Otsuka's knowledge of prior art work conducted by Parke Davis. Finally, Defendants have asked Otsuka to bring K. Minamikawa, a Japanese citizen, and two Finnegan partners, Charles Van Horn and Thomas Irving, to trial to testify regarding the original prosecution and reexamination of the '528 patent.

Defendants reserve the right to amend and update this list to rebut any unanticipated evidence or argument Otsuka may raise at trial. To the extent permitted by the Federal Rules of Civil Procedure, Defendants also reserve the right to introduce the prior sworn testimony (e.g. deposition testimony) of any witness who has provided sworn testimony in this action (or any other action) including, but not limited to, those named below. Defendants also reserve the right to call other witnesses at trial if Otsuka calls or brings to trial witnesses that it has not identified in this order. *Any amendment to this Final Pretrial Order would be subject to a showing of manifest injustice.*

Defendants may call the following witnesses at trial:

1. Yasuo Oshiro

Dr. Oshiro, one of the named co-inventors on the '528 patent and an Otsuka Rule 30(b)(6) witness, will generally testify about the development of aripiprazole while a researcher

with Otsuka. He will provide testimony about his education and experience at the time aripiprazole was developed. His testimony will include his work on the OPC 4000 series compounds, the OPC 14000 series compounds, and the methods used and route taken to arrive at aripiprazole. He will also testify as to the role played by other Otsuka researchers in the development and testing of CNS compounds. He is expected to testify about the various animal tests used at Otsuka to screen compounds for antipsychotic activity. Dr. Oshiro will testify about his involvement in the prosecution of the '528 patent including the tests results reported in the '528 patent as well as those submitted with his declaration to the Patent Office during the original prosecution of the '528 patent. He will testify that after he joined the Otsuka IP department in 1998, the '528 patent was reexamined. He will also testify regarding his preparation of various articles published by Otsuka regarding carbostyryl derivatives. Dr. Oshiro is also expected to testify regarding research conducted in the 1986-1988 timeframe to obtain information on what other companies were doing in anti-schizophrenic research including work being done by Parke-Davis on coumarin derivatives. Dr. Oshiro may also testify on other subject matters addressed during his deposition. Dr. Oshiro will also provide foundational testimony to support the authenticity and admissibility of Otsuka documents including documents introduced during his deposition.

2. Tsuyoshi Hirose

Mr. Hirose will testify generally regarding his involvement with aripiprazole both as a researcher at Otsuka and as the current head of the aripiprazole group. He may also testify regarding the role of others at Otsuka involved in the development and testing of CNS compounds including aripiprazole. He will testify regarding the various animal screening tests employed by Otsuka to evaluate compounds including the use of the mouse jumping test to screen compounds for antipsychotic activity. He will also testify about the anti-apomorphine stereotypy test and the anti-epinephrine lethality animal tests used to screen antipsychotic compounds. He will also discuss his involvement in obtaining the '528 patent including the preparation of his declaration submitted to the patent office during the reexamination of the '528 patent. He is expected to testify regarding the testing conducted for his declaration. In addition to testifying regarding the contents of his declaration, he will also identify data and documents supplemental to the data used in his declaration. Mr. Hirose may also testify on other subject matters addressed during his deposition. Mr. Hirose will also provide foundational testimony to support the authenticity and admissibility of Otsuka documents and other documents introduced during his deposition.

3. Carol A. Tamminga, M.D.

Dr. Tamminga will testify about the symptoms of schizophrenia, the history of the treatment of schizophrenia, the side-effects of various anti-schizophrenic drugs and the animal modeling and treatment of negative symptoms of schizophrenia.

4. Lawrence D. Wise, Ph.D.

Dr. Wise will testify to facts establishing the authenticity and prior art status of a poster he presented at the Society for Neurosciences meeting ("1987 Neuroscience Meeting") in

Louisiana. In 1987, Dr. Wise was a Senior Research Assistant for the Warner-Lambert Company. Dr. Wise will testify that he authored, prepared and presented a poster at the 1987 Neurosciences Meeting reporting his work at Warner Lambert on PD-116795 and related compounds. He gave a three-hour poster presentation during a session at the 1987 Neuroscience Meeting devoted to drugs for the treatment of schizophrenia. During the poster presentation, he displayed a large version of his poster and distributed smaller copies of his poster to attendees. Dr. Wise will authenticate a copy of his poster presented at the 1987 Neurosciences Meeting obtained from his personal records. Dr. Wise may also testify on other subject matters addressed during his deposition.

5. Nicholas Bodor

Mr. Bodor testified as an Otsuka expert witness in connection with an interference proceeding in the Patent Office involving the Banno '416 patent. Defendants have designated portions of Mr. Bodor's sworn testimony relevant to the disclosure and teaching of the Banno '416 patent as it relates to the person of ordinary skill in the art's expectations regarding carbostyryl derivatives and near-carbostyryl derivatives for antipsychotic use.

6. Subject to Otsuka's willingness to bring the requested fact witnesses to trial, Defendants may call the following witnesses by deposition, who will testify: Kazuo Banno, Takafuni Fujioka, Arthur Garrett, Anthony Hartmann, Takashi Hiyama, Asami Isoyama, Kaneshige Kajii, Keiji Kakumoto, Tetsuro Kikuchi, Hisashi Kitagawa, Nobuyuki Kurahashi, Adam Lenkowsky, Kasuma Mallikaarjun, Noriyuki Mamiya, William McHale, Takashi Miwa, Kazuyuki Nakagawa, Masaaki Osaki, Seiji Sato, Sheldon Beshad, Yuko Soneoka, Shigeo Suzuki, Katsumi Tamura, Tatsuyoshi Tanaka, Katsura Tottori, Masahiro Tsutsui, Yasufumi Uwahodo, Charles Van Horn, Shuji Yamashita, Thomas Irving, K. Minamikawa, Shinichiro Haruki.

Defendants designation of deposition testimony of the above-identified witnesses in set forth in the attached Defendants' Deposition Designations.

To the extent that objections to the English translation of foreign language trial exhibits cannot be resolved in advance of trial, Defendants' will have available and may call the following witnesses in connection with their English translations of various foreign language trial exhibits including testimony necessary to resolve any objections that Plaintiff may raise at trial regarding the English translation of any Japanese language trial exhibit:

1. Mr. Charles Aschmann
Park IP Translations
134 West 29th Street, 5th Floor

New York, NY 10001

2. Mr. John F. Bukacek
6171 N. Sheridan Road, Suite 2212
Chicago, IL 60660-5841

B. On damages defendants intend to call the following witnesses who will testify in accordance with the following summaries:

Defendants reserve their right to seek their costs and attorney fees pursuant to, inter alia, 35 U.S.C. § 285.

C. Plaintiff objects to the following witnesses for the reasons stated:

Defendants have requested that certain witnesses appear at trial, namely Y. Oshiro, S. Sato, N. Kurahashi, S. Haruki, K. Minamikawa, T. Hiyama, T. Kikuchi, T. Hirose, C. Van Horn, and T. Irving. With respect to the additional witnesses identified in this Pretrial Order, Defendants have indicated they only seek to introduce deposition testimony.

Otsuka has agreed to bring Dr. Oshiro, Dr. Hirose and Mr. Van Horn to testify live at trial, but Otsuka does not concede that their testimony will be relevant to the defenses and counterclaims Defendants intend to pursue at trial. Otsuka further objects to all of the witnesses identified by Defendants (whether as witnesses requested to appear to testify live at trial or via deposition testimony) under FRE 501 to the extent Defendants seek testimony protected by the attorney-client privilege and/or work-product immunity.

As discussed during the Pretrial Conference, Otsuka will not bring to trial the remaining witnesses Defendants request appear at trial based on the following objections:

1. S. Sato -- Otsuka objects to Defendants' request that S. Sato appear at trial under FRE 401, 402 and 403. Defendants have not adequately explained how Dr. Sato's testimony would be relevant to any of their defenses, why they could not obtain equivalent testimony from

another live witness and/or why Defendants cannot rely on Dr. Sato's deposition testimony. Moreover, Dr. Sato is a Japanese citizen, residing in Japan, and it would be a significant and unnecessary burden for him to travel to the United States for trial. This burden outweighs any alleged need for Dr. Sato to appear to testify live at trial.

2. N. Kurahashi -- Otsuka objects to Defendants' request that N. Kurahashi appear at trial under FRE 401, 402 and 403. Defendants have not adequately explained how Mr. Kurahashi's testimony would be relevant to any of their defenses, why they could not obtain equivalent testimony from another live witness and/or why Defendants cannot rely on Mr. Kurahashi's deposition testimony. Moreover, Mr. Kurahashi is a Japanese citizen, residing in Japan, and it would be a significant and unnecessary burden for him to travel to the United States for trial. This burden outweighs any alleged need for Mr. Kurahashi to appear to testify live at trial.

3. S. Haruki -- Otsuka objects to Defendants' request that S. Haruki appear at trial under FRE 401, 402 and 403. Defendants never sought to depose S. Haruki during fact discovery despite having ample opportunity to do so, and Defendants have not adequately explained how his testimony would be relevant to any of their defenses. Moreover, S. Haruki is a Japanese citizen, residing in Japan, and it would be a significant and unnecessary burden for him to travel to the United States for trial. This burden outweighs any alleged need for S. Haruki to appear to testify live at trial.

4. K. Minamikawa -- Otsuka is unaware of any individual named "K. Minamikawa." To the extent Defendants seek testimony from Dr. Saeko Minamikawa, Otsuka objects based on FRE 401, 402, 403 and 501. Defendants never sought to depose Dr. Minamikawa during fact discovery despite having ample opportunity to do so, and Defendants have never explained how

her testimony would be relevant to any of their defenses. Indeed, to the extent Dr. Minamikawa does have any information relevant to Defendants' defenses, that would be privileged given her role in Otsuka's Intellectual Property Department. Moreover, Dr. Minamikawa is a Japanese citizen, residing in Japan, and it would be a significant and unnecessary burden for her to travel to the United States for trial. This burden outweighs any alleged need for Dr. Minamikawa to appear to testify live at trial.

5. T. Hiyama -- Otsuka objects to Defendants' request that T. Hiyama appear at trial under FRE 401, 402 and 403. Defendants have not adequately explained how Dr. Hiyama's testimony would be relevant to any of their defenses, why they could not obtain equivalent testimony from another live witness and/or why Defendants cannot rely on Dr. Hiyama's deposition testimony. Moreover, Dr. Hiyama is a Japanese citizen, residing in Japan, and it would be a significant and unnecessary burden for him to travel to the United States for trial. This burden outweighs any alleged need for Dr. Hiyama to appear to testify live at trial.

6. T. Kikuchi -- Otsuka objects to Defendants' request that T. Kikuchi appear at trial under FRE 401, 402 and 403. Defendants have not adequately explained how Dr. Kikuchi's testimony would be relevant to any of their defenses, why they could not obtain equivalent testimony from another live witness and/or why Defendants cannot rely on Dr. Kikuchi's deposition testimony. Moreover, Dr. Kikuchi is a Japanese citizen, residing in Japan, and it would be a significant and unnecessary burden for him to travel to the United States for trial. This burden outweighs any alleged need for Dr. Kikuchi to appear to testify live at trial.

7. T. Irving -- Otsuka objects to Defendants' request that Mr. Irving appear at trial under FRE 401, 402, 403 and 501. Defendants never sought to depose Mr. Irving during fact discovery despite having ample opportunity to do so, and Defendants have never explained how

his testimony would be relevant to any of their defenses. Indeed, to the extent Mr. Irving does have any information relevant to Defendants' defenses, that would be privileged given the fact that he was previously patent counsel for Otsuka on matters unrelated to the present litigation.

Otsuka objects to the witnesses Defendants intend to testify by deposition for the reasons stated in Otsuka's objections to Defendants' deposition designations, using the codes set forth below in Otsuka's objections to Defendants' trial exhibits. To the extent Defendants later indicate they wish to request any of these witnesses appear live at trial, Otsuka reserves the right to assert any additional objections.

Otsuka also objects to Defendants' efforts to include deposition testimony provided by Dr. Nicholas Bodor⁸ in an interference proceeding during the prosecution of the application which led to the '416 patent. Defendants should be precluded from using Dr. Bodor's testimony at trial at least for the following reasons: (1) Dr. Bodor's prior testimony has no bearing on the present action and involved different parties and (2) Dr. Bodor's testimony is inadmissible under FRCP 26(a)(2), FRCP 32(a)(8) and FRE 802.

Otsuka also objects to Defendants' efforts to call Dr. Wise to testify live at trial. Dr. Wise was belately identified as a live witness and his testimony is also not relevant to any issue in this case. Defendants seek to have Dr. Wise testify as to the authenticity of a poster allegedly presented by Dr. Wise. Because counsel for Defendants instructed Dr. Wise to not answer questions at his deposition concerning the authenticity of this poster, Dr. Wise should likewise not be permitted to testify in this regard at trial.

⁸ Defendants state that they seek to call Dr. Bodor to testify solely via his previously recorded testimony. Otsuka therefore objects to Defendants' confusing inclusion of an alleged description of this testimony in the section describing live fact witnesses.

8. EXPERT WITNESSES (No opposing counsel shall be permitted to question the expert's qualifications unless the basis of an objection is set forth herein).

A. Plaintiff's expert witnesses are:

Defendants have stipulated to infringement of the asserted claims 12, 17 and 23 of the '528 patent and therefore Otsuka need not prove infringement at trial. Moreover, as the '528 patent is presumed valid, Otsuka has no burden of proof regarding Defendants' affirmative defenses and counterclaims that the asserted claims of the '528 patent are invalid or unenforceable. Defendants alone must prove these affirmative defenses and counterclaims by clear and convincing evidence. Without assuming any burden of proof, Otsuka expects that it may call the following expert witnesses in person in response to Defendants' affirmative defenses and counterclaims of invalidity and/or unenforceability. To the extent permitted by the Federal Rules of Evidence, Otsuka also reserves the right to introduce the prior sworn testimony (e.g., deposition testimony) of any witness named below:

1. Dr. Carol A. Tamminga

Dr. Tamminga is a Professor of Psychiatry and Chief of Translational Neuroscience Research at the University of Texas Southwestern Medical School in Dallas, Texas. She is a medical doctor with more than 30 years of experience in the field of psychiatry. Her work has focused on schizophrenia and clinical evaluations of antipsychotic drugs. She has conducted numerous clinical trials of antipsychotic drugs, and her clinical experience has included observing patients treated with aripiprazole (Abilify®). Dr. Tamminga has edited scientific journals relating to schizophrenia, held numerous positions in organizations dedicated to the study of schizophrenia, and published more than 300 papers and two books in the areas of psychopharmacology, neuroscience, and schizophrenia, including antipsychotic agents, their mechanism of action, and side effects. Dr. Tamminga has been appointed to several federal

scientific advisory boards, including the FDA's Psychopharmacological Drugs Advisory Committee, and she has received numerous awards for her work relating to schizophrenia. Dr. Tamminga testified in the *Janssen* case relating to the antipsychotic drug risperidone, and this Court relied upon her testimony in rendering its decision. *See, e.g., Janssen*, 456 F. Supp. 2d at 648-50, 664, 670, 672.

2. Dr. Bryan L. Roth

Dr. Roth is a Professor of Pharmacology and Medicinal Chemistry at the University of North Carolina-Chapel Hill Medical School. He is a medical doctor who also holds a Ph.D. degree in Biochemistry. Dr. Roth has given more than 200 invited talks in the areas of psychopharmacology, neuropharmacology, psychiatry, pharmacology, and neuroscience. He has extensive knowledge of antipsychotic drug screening methods, including assays used to predict antipsychotic activity. He also has experience with antipsychotic clinical trials and treating patients suffering from schizophrenia. For the past ten years, Dr. Roth has directed the National Institute of Mental Health Psychoactive Drug Screening Program. He also serves as the Principal Investigator of the National Cooperative Drug Discovery Group, a venture funded by the NIH devoted to understanding antipsychotic drug actions. Dr. Roth has published more than 250 papers and two books relating to psychopharmacology, neuroscience, atypical antipsychotics and their mechanisms of action, neurotransmitters and receptors in the brain, and the development of screening methods for CNS drug discovery. He has conducted scientific research relating to aripiprazole and published comprehensive studies of aripiprazole's pharmacology. Dr. Roth has received numerous honors and awards for his research in schizophrenia.

3. Dr. David E. Nichols

Dr. Nichols is a professor at Purdue University. He holds the Robert C. and Charlotte P. Anderson Distinguished Chair in Pharmacology and also is a Professor of Medicinal Chemistry and Molecular Pharmacology. Dr. Nichols has taught and performed scientific research in the fields of medicinal chemistry and pharmacology for more than 35 years. His teaching has included graduate courses in drug design. In 1976, he began teaching a graduate course on drugs affecting the central nervous system, including drugs for the treatment of schizophrenia. His research has focused on the relationship between the chemical structure of a molecule and its effects on biological systems, including the design of molecules targeted to receptors and uptake carriers for dopamine and serotonin. Dr. Nichols has published 240 scientific articles and several book chapters and monographs, and he was elected to membership in the American College of Neuropsychopharmacology, a prestigious neuropharmacology society that includes relatively few medicinal chemists within its ranks. Dr. Nichols testified in the *Eli Lilly* case relating to the antipsychotic drug olanzapine, and the district court relied up his testimony in rendering its decision. *See, e.g., Eli Lilly*, 364 F. Supp. 2d at 832-34, 841-52, 860, 895.

4. Dr. Paul A. Bartlett

Dr. Bartlett is a Professor of Chemistry, Emeritus, at the University of California, Berkeley. He began teaching at Berkeley in 1973 and was Chair of the Chemistry Department from 1996 to 2000. Dr. Bartlett has lectured on drug design, and he co-founded a successful start-up company engaged in drug discovery. He has co-authored more than 180 articles and abstracts in the fields of organic chemistry, bioorganic chemistry, and drug design, and he is named as co-inventor on several U.S. patents. Dr. Bartlett is a member of the editorial board of ChemMedChem, an international journal devoted to drug discovery. Dr. Bartlett has received

several awards, including the Cope Scholar Award from the American Chemical Society. He was elected a Fellow in the American Academy of Arts and Sciences in 1994.

5. Dr. Ronald A. Thisted

Dr. Thisted is a professor who serves as the Chairman of the Department of Health Studies at the University of Chicago. He is an expert in the fields of statistics and biostatistics, including statistical methods used in the fields of medicine, biology, and pharmaceutical sciences. Dr. Thisted has been a member of the faculty of the University of Chicago since 1976 and a member of the faculty of the University of Chicago Pritzker School of Medicine since 1989. He has written over 90 scientific articles, 25 book chapters, and one book in the field of statistical computation. Dr. Thisted was elected a Fellow of the American Association for the Advancement of Science in 1992 and a Fellow of the American Statistical Association in 1988. Dr. Thisted testified in the *Eli Lilly* case, and the district court relied up his testimony in rendering its decision. *See, e.g., Eli Lilly*, 364 F. Supp. 2d at 855, 858-59, 861-65, 868, 885-88, 890-92, 918.

6. Richard A. Killworth

Mr. Killworth is an expert in the field of patent practice and procedure. He has worked as a patent attorney for more than 35 years. In the late 1960s, Mr. Killworth worked as a Patent Examiner in the organic chemistry group at the PTO while attending George Washington University Law School. After graduating with honors, he served as a law clerk to Judge J. Lindsay Almond, Jr. of the U.S. Court of Customs and Patent Appeals, a predecessor to the U.S. Court of Appeals for the Federal Circuit. He received an L.L.M. degree in patent and trade regulation law from George Washington University in 1972. Mr. Killworth has been in private patent practice since September 1972. He currently is a partner with Dinsmore & Shohl, L.L.P. His practice has included the prosecution of hundreds of patent applications. He has taught law

school and CLE courses in patent practice and procedure and has published extensively in those fields. Mr. Killworth has testified as an expert in patent practice and procedure in several district court patent litigations, including the *Eli Lilly* case in which his testimony was relied upon by the district court in rendering its decision. *See, e.g., Eli Lilly*, 364 F. Supp. 2d at 835-37, 840-41, 859, 873, 894-95.

7. John C. Jarosz

Mr. Jarosz is an economist who specializes in the valuation of intellectual property. He is a Managing Principal of Analysis Group, Inc., an economic, financial, and strategy consulting firm. Mr. Jarosz serves as Director of the firm's Washington, D.C. office. He has conducted more than 250 economic analyses in a range of industries, including pharmaceutical products. He has published and spoken extensively on economic issues relating to patents and other intellectual property. Mr. Jarosz also has testified as an expert on patent damages and other economic issues in numerous district court litigations.

B. Defendants' objections to the qualifications of plaintiff's expert are:

Defendants' object to some of the proposed expert witnesses identified by Plaintiff as addressed below under Fed. R. Evid. 401 and 402. Defendants' further object to Plaintiff's proposed expert witnesses under Fed. R. Evid. 403 in that much of the testimony to be provided by Plaintiff's experts, as disclosed in their respective expert reports, is a needless presentation of cumulative evidence and will result in a waste of time at trial. Defendants' further object to Plaintiff's identified expert witnesses under Fed. R. Evid. 702 as not qualified by education, training or experience to testify as an expert in relation to any relevant matter in this case and their proposed expert opinions do not satisfy the other requirements of Fed. R. Evid. 702. Therefore, any testimony that they might provide would not be reliable, relevant or otherwise admissible.

Defendants provide the following additional specific objections to Plaintiff's expert witnesses:

1. Dr. Paul A. Bartlett – Defendants object to Dr. Bartlett as an expert witness for Plaintiff under Fed. R. Evid. 401, 402, 403 and 702. Dr. Bartlett is a retired bioorganic chemistry professor. Dr. Bartlett studied how to design molecules with biological activity, in particular peptidomimetics, molecules that imitate proteins, especially related to plant biochemistry. None of his research at Berkeley involved antipsychotics, he has no experience researching antipsychotic drugs, and to the extent that he did consulting, he does not remember any details about CNS compounds. Dr. Bartlett is not a psychiatrist (or medical doctor of any kind), medicinal chemist or statistician, and he lacks any expertise or experience in the field of antipsychotic drug discovery. He is therefore not qualified by either education, training or experience to testify as an expert witness on psychiatry, neurobiology, schizophrenia, the discovery or development of antipsychotic drugs, clinical studies of humans relating to antipsychotic drugs, efficacy or side effects of antipsychotic drugs, animal models used to identify potential antipsychotic drugs, clinical pharmacology, statistics, or the alleged non-obviousness of aripiprazole (including the scope and content of the prior art, the level of skill in the art, the differences between the claimed invention and the prior art, and objective evidence of nonobviousness). Dr. Bartlett is also not qualified by education or experience to give expert testimony concerning the materiality, lack of materiality or cumulativeness of any information withheld or misrepresented to the PTO during the original prosecution and reexamination of the '528 patent or any alleged intent to deceive the PTO. For these reasons, Defendants object to any proposed expert testimony by Dr. Bartlett.

2. John C. Jarosz – Defendants object to Mr. Jarosz as an expert witness for Plaintiff on the issue of commercial success under Fed. R. Evid. 401, 402, 403 and 702. The issue of commercial success under the facts in this action are not relevant to the issue of the nonobviousness of the '528 patent by virtue of established Federal Circuit precedent. Further, the methodology employed by Mr. Jarosz in assessing commercial success lacks the requisite nexus to the claimed benefits of the asserted claims of the '528 patent and is based upon insufficient facts or data and is not the product of reliable principles and methods.

3. Dr. David E. Nichols - Defendants object to Dr. Nichols as an expert witness for Plaintiff under Fed. R. Evid. 401, 402, 403 and 702. Dr. Nichols has an undergraduate degree in chemistry and a Ph.D. in medicinal chemistry. Dr. Nichols is not a psychiatrist (or medical doctor of any kind), pharmacologist, or statistician, and he lacks specific expertise or experience in the field of antipsychotic drug discovery. He is therefore not qualified by education, training or experience to testify as an expert witness on psychiatry, neurobiology, schizophrenia, the discovery or development of antipsychotic drugs, clinical studies in humans relating to antipsychotic drugs, the efficacy or side effects of antipsychotic drugs, animal models used to identify potential antipsychotic drugs, pharmacology (including clinical or behavioral pharmacology), statistics, or the alleged nonobviousness of aripiprazole (including the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed invention and the prior art, or objective evidence of nonobviousness). Dr. Nichols is also not qualified by education, training or experience to give expert testimony concerning the materiality, lack of materiality or the cumulativeness of any information alleged withheld from the PTO during the prosecution and reexamination of the '528 patent, or any lack of intent to

deceive the PTO. For these reasons, Defendants object to any proposed expert testimony by Dr. Nichols.

4. Dr. Bryan L. Roth - Defendants object to Dr. Roth as an expert witness for Plaintiff under Fed. R. Evid. 401, 402, 403 and 702. Dr. Roth has an undergraduate degree in biology and graduate degrees in biochemistry. Dr. Roth is not a pharmacologist, or statistician, and he lacks specific expertise or experience in the field of antipsychotic drug discovery. He is therefore not qualified by education, training or experience to testify as an expert witness on psychiatry, neurobiology, schizophrenia, the discovery or development of antipsychotic drugs, clinical studies in humans relating to antipsychotic drugs, the efficacy or side effects of antipsychotic drugs, animal models used to identify potential antipsychotic drugs, pharmacology (including clinical or behavioral pharmacology), statistics, or the alleged nonobviousness of aripiprazole (including the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed invention and the prior art, or objective evidence of nonobviousness). Dr. Roth is also not qualified by education, training or experience to give expert testimony concerning the materiality, lack of materiality or the cumulateness of any information alleged withheld from the PTO during the prosecution and reexamination of the '528 patent, or any lack of intent to deceive the PTO. For these reasons, Defendants object to any proposed expert testimony by Dr. Roth.

5. Dr. Ronald A. Thisted - Defendants object to Dr. Thisted as an expert witness for Plaintiff under Fed. R. Evid. 401, 402, 403 and 702. Dr. Bartlett has a Ph.D in statistic and his primary education, training and experience is in mathematics and statistics. As such, Dr. Thisted has no specific education, experience or training with respect to analyzing the specific test results at issue in this action. Dr. Thisted is not a psychiatrist (or medical doctor of any kind),

pharmacologist or chemist and lacks any expertise or experience in the field of antipsychotic drug discovery. Dr. Thisted is not qualified by education, training or experience to testify as an expert witness on the various animal models involved in this action, on animal models used to identify potential antipsychotic drugs, on psychiatry, neurobiology, schizophrenia, the discovery or development of antipsychotic drugs, clinical studies in humans relating to antipsychotic drugs, the interpretation of animal tests in screening for antipsychotic activity, the efficacy or side effects of antipsychotic drugs, pharmacology (including clinical or behavioral pharmacology) or the alleged nonobviousness of aripiprazole (including the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed invention and the prior art, or objective evidence of nonobviousness). Dr. Thisted is not qualified to give expert testimony concerning the materiality, lack of materiality or cumulativeness of any information withheld from or misrepresented to the PTO during the prosecution or reexamination of the '528 patent or the intent or lack of intent to deceive the PTO. For these reasons, Defendants object to any proposed expert testimony by Dr. Thisted.

C. Defendants' expert witnesses are:

1. Defendants Teva and Barr

a. Jeffrey B. Press, Ph.D.

Dr. Press is the Managing Partner of Press Consulting Partners, in which he offers his extensive experience in developing antipsychotic drugs to pharmaceutical companies. He is a medicinal chemist with over 30 years of experience in the field. His work has focused on synthesizing and characterizing novel drug compounds, including antipsychotic drugs. Dr. Press's work in the pharmaceutical industry often involved collaborating with pharmacologists to assess the antipsychotic activity and side effect liabilities of compounds using animal models.

His has also helped pharmaceutical companies prepare compounds for clinical trials. Dr. Press has authored close to 100 peer-reviewed papers and book chapters regarding medicinal chemistry and the development of drugs, including antipsychotic drugs, and has been named an inventor on more than 50 issued patents, many of which are directed to therapeutic agents, including CNS agents. Dr. Press has also served on several editorial boards of journals involving medicinal chemistry and pharmaceutical patents.

b. Richard J. Beninger, Ph.D.

Dr. Beninger is a Professor of Psychology and Psychiatry at Queens College. He is a pharmacologist with over 30 years of experience in the field. His work has focused on the evaluation of the role of dopamine and the various dopamine receptors in behavior by using dopamine agonists and antagonists in animal models, including models indicative of antipsychotic activity and side effects. Dr. Beninger has authored numerous peer-reviewed papers and book chapters regarding the mechanisms of CNS agents, including antipsychotic drugs. He has also refereed publications involving neuropharmacology, neurotoxicity, and schizophrenia. Dr. Beninger gives lectures and presentations in these subject areas, including presentations involving the mechanisms underlying antipsychotic action.

c. John T. Goolkasian

Mr. Goolkasian is an expert in the field of patent practice and procedure. He has worked about 25 years for the PTO. At the PTO, Mr. Goolkasian served as an Administrative Patent Judge, and has made the PTO's final determination of patentability in contested cases more than 3,000 times. He has also served in the PTO as Examiner, Supervisory Primary Examiner, Instructor, and Chief Instructor at the Patent Academy (a school established by the PTO to teach patent practice and procedure). Outside of working at the PTO, Mr. Goolkasian has prosecuted

numerous patent applications at major law firms and written numerous validity and infringement opinions for corporations and the United States Department of Justice. He received his juris doctorate from Georgetown University's Law School.

2. Defendant Apotex

a. Professor Neal Castagnoli, Ph.D.

Neal Castagnoli is the Peters Professor of Chemistry Emeritus at Virginia Polytechnic Institute and State University ("Virginia Tech"). He is recognized as an expert in organic and medicinal chemistry, drug metabolism, biochemical toxicology and bioanalytical chemistry. His research has focused on compounds related to the brain's portions that involve the chemical dopamine. He has published extensively on the antipsychotic haloperidol.

During his long career he has published extensively. In conducting his research he has engaged in extensive design and synthesis of chemical compounds. Analyzing the relationship of chemical structure to biological activity is a central activity in his research.

While a professor at the University of California, San Francisco, he taught courses in organic chemistry and medicinal chemistry. During this period he worked closely with clinical pharmacologists. During his time at Virginia Tech, he has been a professor in the Harvey W. Peters Research Center, a research center dedicated to understanding the chemical and biochemical features of central nervous system disorders

He has consulted extensively over the years with the pharmaceutical industry on issues involving drug design. He has worked on over 50 research projects directed to drug discovery and development. About 10 of those 50 projects focused on agents that act on the brain.

In 2009, Professor Castagnoli was a member of the inaugural class of American Chemical Society Fellows, recognizing his true excellence in chemistry along with his distinctive service to the world of chemistry.

b. John F. Marshall, Ph.D.

John F. Marshall, is a Professor of Neurobiology & Behavior at the University of California, Irvine, where he has been studying the influences of dopamine on brain and behavior in animals since 1977. Among the projects he has directed during the past 30 years are (i) studies of neuroleptic drugs on dopamine receptors in brain; (ii) the construction and use of behavioral rating scales to measure the effects of specific dopamine D1 and D2 receptor agonists on stereotyped behaviors; (iii) and investigations of how methamphetamine affects the brain. Currently, he serves as Principal Investigator of a grant from the National Institutes of Health to study the potential for brain injury of methamphetamine exposure.

John Marshall has a long and distinguished record of contributions to neuroscience. He is currently on the editorial board of the journal *Behavioral Neuroscience*.

c. John T. Goolkasian

See Section 8.C.1.c., above.

d. Carol A. Tamminga, M.D.

See Section 8.A.1., above.

In addition, each defendant reserves the right to rely, in whole or in part, on any testimony of the expert witnesses for the other defendants.

D. Plaintiff's objections to the qualifications of defendants' experts are:

Otsuka objects to all of the proposed expert witnesses identified by Defendants on the following grounds. Otsuka objects to all of the proposed expert witnesses identified by Defendants (except for Otsuka's expert, Dr. Tamminga) under FRE 401, 402, and 403 to the

extent their intended testimony is not relevant to Defendants' defenses and counterclaims. Otsuka further objects to these witnesses under FRE 702 as they are not qualified to testify as an expert in relation to any relevant matter in this case and their proposed expert opinions do not satisfy the other requirements of FRE 702. Therefore any testimony that they might provide would not be reliable, relevant or otherwise admissible.

Otsuka provides the following additional specific objections to the witnesses Defendants request appear at trial:

1. Dr. Richard Beninger -- Otsuka objects to Dr. Beninger as an expert witness for Defendants Teva and Barr under FRE 401, 402, 403 and 702. Dr. Beninger is a psychologist who has used rats to study the role of neurotransmitters in reward-related incentive learning. There is no issue in this case relating to psychology or reward-related incentive learning. Dr. Beninger is not a psychiatrist (or medical doctor of any kind), medicinal chemist, or statistician, and he lacks any expertise or experience in the field of antipsychotic drug discovery. He is therefore unqualified to testify as an expert witness on psychiatry, neurobiology, schizophrenia, the discovery or development of antipsychotic drugs, clinical studies in humans relating to antipsychotic drugs, the efficacy or side effects of antipsychotic drugs, medicinal chemistry, animal models used to identify potential antipsychotic drugs, clinical pharmacology, statistics, or the alleged obviousness of aripiprazole (including the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed invention and the prior art, and objective evidence of nonobviousness). Dr. Beninger is also unqualified to give expert testimony concerning the materiality of any information allegedly withheld from or misrepresented to the PTO during the prosecution or reexamination of the '528 patent or any

alleged intent to deceive the PTO. For these reasons, Otsuka objects to any proposed expert testimony by Dr. Beninger.

2. Dr. Jeffery Press -- Otsuka objects to Dr. Press as an expert witness for Defendants Teva and Barr under FRE 401, 402, 403 and 702. Dr. Press is a patent litigation consultant with a chemistry background. His limited experience in antipsychotic drug research ended more than 25 years ago (in 1983). Dr. Press is not a psychiatrist (or medical doctor of any kind), pharmacologist, or statistician. He is therefore unqualified to testify as an expert witness on psychiatry, neurobiology, schizophrenia, the discovery or development of antipsychotic drugs, clinical studies in humans relating to antipsychotic drugs, the efficacy or side effects of antipsychotic drugs, animal models used to identify potential antipsychotic drugs, pharmacology (including clinical or behavioral pharmacology), statistics, or the alleged obviousness of aripiprazole (including the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed invention and the prior art, and objective evidence of nonobviousness). Dr. Press is also unqualified to give expert testimony concerning the materiality of any information allegedly withheld from or misrepresented to the PTO during the prosecution or reexamination of the '528 patent or any alleged intent to deceive the PTO. For these reasons, Otsuka objects to any proposed expert testimony by Dr. Press.

3. Dr. John Marshall -- Otsuka objects to Dr. Marshall as an expert witness for Apotex under FRE 401, 402, 403 and 702. Dr. Marshall is a neuroscientist who has used animal models to study the capacity of the central nervous system to regenerate following injury. There is no issue in this case relating to the regeneration of the central nervous system. Dr. Marshall is not a psychiatrist (or medical doctor of any kind), medicinal chemist, or statistician, and he lacks any expertise or experience in the field of antipsychotic drug discovery. He is therefore

unqualified to testify as an expert witness on psychiatry, human neurobiology, schizophrenia, the discovery or development of antipsychotic drugs, clinical studies in humans relating to antipsychotic drugs, the efficacy or side effects of antipsychotic drugs, medicinal chemistry, animal models used to identify potential antipsychotic drugs, clinical pharmacology, statistics, or the alleged obviousness of aripiprazole (including the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed invention and the prior art, or objective evidence of nonobviousness). Dr. Marshall is also unqualified to give expert testimony concerning the materiality of any information allegedly withheld from or misrepresented to the PTO during the prosecution or reexamination of the '528 patent or any alleged intent to deceive the PTO. For these reasons, Otsuka objects to any proposed expert testimony by Dr. Marshall.

4. Dr. Neal Castagnoli -- Otsuka objects to Dr. Castagnoli as an expert witness for Apotex under FRE 401, 402, 403 and 702. Dr. Castagnoli is a chemist who has studied the interaction of monoamine oxidase and other brain enzymes and receptors with respect to neuroprotection and neurotoxicity in the central nervous system. There are no issues in this case relating to monoamine oxidase, neuroprotection, or neurotoxicity. Dr. Castagnoli is not a psychiatrist (or medical doctor of any kind), pharmacologist, or statistician, and he lacks any expertise or experience in the field of antipsychotic drug discovery. He is therefore unqualified to testify as an expert witness on psychiatry, neurobiology, schizophrenia, the discovery or development of antipsychotic drugs, clinical studies in humans relating to antipsychotic drugs, the efficacy or side effects of antipsychotic drugs, animal models used to identify potential antipsychotic drugs, pharmacology (including clinical or behavioral pharmacology), statistics, or the alleged obviousness of aripiprazole (including the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed invention and the prior art, or

objective evidence of nonobviousness). Dr. Castagnoli is also unqualified to give expert testimony concerning the materiality of any information allegedly withheld from or misrepresented to the PTO during the prosecution or reexamination of the '528 patent or any alleged intent to deceive the PTO. For these reasons, Otsuka objects to any proposed expert testimony by Dr. Castagnoli.

5. Mr. John Goolkasian -- Otsuka objects to any proposed expert testimony by Mr. Goolkasian under FRE 401, 402, 403 and 702, other than testimony concerning routine practices and procedures before the PTO. Mr. Goolkasian is a patent attorney who holds an undergraduate degree in chemical engineering and no advanced technical degree. Mr. Goolkasian is not a psychiatrist (or medical doctor of any kind), medicinal chemist, pharmacologist, or statistician, and he lacks any expertise or experience in the field of antipsychotic drug discovery. He is therefore unqualified to testify as an expert witness on psychiatry, neurobiology, schizophrenia, the discovery or development of antipsychotic drugs, clinical studies in humans relating to antipsychotic drugs, the efficacy or side effects of antipsychotic drugs, medicinal chemistry, animal models used to identify potential antipsychotic drugs, pharmacology (including clinical or behavioral pharmacology), statistics, or the alleged obviousness of aripiprazole (including the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed invention and the prior art, or objective evidence of nonobviousness). Mr. Goolkasian is also unqualified to give expert testimony concerning the materiality of any information allegedly withheld from or misrepresented to the PTO during the prosecution or reexamination of the '528 patent or any alleged intent to deceive the PTO. For these reasons, Otsuka objects to any proposed expert testimony by Mr. Goolkasian other than testimony concerning routine practices and procedures before the PTO.

6. Dr. Carol Tamminga -- Otsuka objects to the Defendants' efforts to call Otsuka's expert, Dr. Tamminga, as either a fact or expert witness at trial.

9. PLAINTIFF'S EXHIBITS (Except for exhibits the need for which could not reasonably have been foreseen or which are used solely for impeachment purposes, only the exhibits set forth on the exhibit list attached hereto may be introduced at trial. Any objection to an exhibit, and the reason for said objection, must be set forth below or it shall be deemed waived. All parties hereby agree that it will not be necessary to bring in the custodian of any exhibit as to which no such objection is made).

A. Plaintiff intends to introduce into evidence the exhibits listed on the attached exhibit list (list by number with a description of each):

Otsuka's exhibit list includes Japanese-language documents and also documents in other foreign languages. For all such documents, Otsuka intends to introduce at trial an exhibit including both the original document and an English language translation. Contrary to Defendants' contention, Otsuka has already provided numerous translations of Japanese and foreign language documents to Defendants and may provide additional translations in accordance with the parties' agreement below. Further, Otsuka has not received any revised translations that Defendants have indicated they will be providing.

The parties have agreed to exchange certified translations of all documents they intend to introduce at trial and to work to resolve any objections to those translations by July 7, 2010. For any additional translations that the parties may later determine they will rely on at trial, the parties shall identify and exchange copies of certified translations no later than 6:30 p.m. (EST) six calendar days before the certified translation is expected to be used. If the opposition party disagrees with the accuracy of the translations, the party shall serve corrections by 6:30 p.m. (EST) three calendar days after service. The parties shall meet and confer in an attempt to resolve any disagreements regarding the accuracy of the translation. The parties agree that the foregoing procedure for later identified translations shall only apply to a limited number of

documents, the parties having identified the clear majority of the translations they intend to use at trial by July 7, 2010. This section does not apply to documents to be used for impeachment purposes.

B. Defendants object to the introduction of plaintiff's exhibits (set forth number of an exhibit and grounds for objection):

Defendants' objections to Plaintiff's trial exhibits are included on Plaintiff's Trial Exhibit List according to the key set forth therein. Since Defendants have not yet had time to review the translations received yesterday afternoon from Otsuka, and have not had a chance to review any further translations Otsuka provides, Defendants reserve the right to object to the introduction of translations by Otsuka to the extent they do not comply with the parties' agreement set forth above.

10. DEFENDANTS' EXHIBITS (See instructions above).

A. Defendants intend to introduce into evidence the exhibits listed on the attached exhibit list (list by number with a description of each):

B. Plaintiff objects to the introduction of defendants' exhibits (set forth number of exhibit and grounds for objection):

Pursuant to Fed. R. Civ. P. 26(a)(3), Otsuka reserves for trial all objections under Fed. R. Evid. 402 and/or 403. Otsuka also reserves the right to object to the use or introduction of any exhibit offered by Defendants to the extent that Defendants do not lay a proper foundation for its admission at trial.

While Otsuka has identified preliminary objections to certain exhibits, Otsuka does not believe that rulings on any of these objections are required prior to trial. Otsuka thus reserves the right to assert further objections during trial if and when such exhibits are offered at trial.

Objections to Defendants' trial exhibits are included on Defendants' Trial Exhibit List according to the key set forth therein:

(Copies of exhibits are to be made for opposing counsel, and a bench book of exhibits is to be delivered to the Judge at the start of trial. If counsel desires to display exhibits to the jury, sufficient copies should be available to provide each juror with a copy; alternatively, enlarged photographic or projected copies may be used).

11. PLAINTIFF'S LEGAL ISSUES

1. Defendants have stipulated to infringement of the asserted claims 12, 17 and 23 of the '528 patent and therefore Otsuka need not prove infringement at trial. Moreover, as the '528 patent is presumed valid, Otsuka has no burden of proof regarding Defendants' affirmative defenses and counterclaims that the asserted claims of the '528 patent are invalid or unenforceable. Defendants alone must prove these affirmative defenses and counterclaims by clear and convincing evidence. Without assuming any burden of proof, Otsuka respectfully submits the following list of issues of law that remain to be litigated with respect to Defendants' invalidity and unenforceability claims. Should the Court determine that any issue identified below as an issue of law is more properly considered an issue of fact, it should be so considered.

VALIDITY

2. Whether Defendants can prove by clear and convincing evidence that asserted claims 12, 17, and 23 of the '528 patent are invalid.

3. Whether Defendants can prove by clear and convincing evidence that each of the references upon which they rely to support their obviousness defense qualifies as prior art to the '528 patent under 35 U.S.C. §§ 102/103. *See, e.g., Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568 (Fed. Cir. 1987).

4. Whether Defendants can prove that the level of ordinary skill in the art determined by this Court in *Janssen*, 456 F. Supp. 2d at 654, does not apply to this case.

5. Whether Defendants can prove by clear and convincing evidence that the invention described in the asserted claims of the '528 patent would have been obvious to a

person of ordinary skill in the art at the time the claimed invention was made in light of the scope and content of the prior art, the differences between such claims and the prior art, the level of ordinary skill in the art at the time, and the objective evidence of nonobviousness. 35 U.S.C. §103(a); *see, e.g., Graham v. John Deere Co.*, 383 U.S. 1 (1966); *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353 (Fed. Cir. 2008); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007).

6. Whether, because the '416 patent is prior art to the '528 patent, any obviousness-type double patenting issue is subsumed by the broader statutory inquiry of alleged obviousness under 35 U.S.C. § 103. *See, e.g., Sanofi-Synthelabo v. Apotex Inc.*, 492 F. Supp. 2d 353, 393 (S.D.N.Y. 2007) ("The double-patenting inquiry is subsumed by the broader statutory inquiry pursuant to 35 U.S.C. § 103 because Sanofi's entire '596 patent was prior art at the time the '265 patent issued."), *aff'd*, 550 F.3d 1075 (Fed. Cir. 2008); *In re Jezl*, 396 F.2d 1009, 1013 (C.C.P.A. 1968) ("The view we take renders it unnecessary to consider at length the double patenting rejection advanced by the board."); *In re Ornitz*, 376 F.2d 330, 334 (C.C.P.A. 1967) ("Where it is possible to conduct the broader inquiry permitted by sections 102(e) and 103 because the references are 'prior art,' it does not make sense to resort to the narrower inquiry which underlies a 'double patenting' rejection."); *In re Land*, 368 F.2d 866, 884 (C.C.P.A. 1966) ("As to the claims on which we have reversed the obviousness rejection, a fortiori this double patenting rejection, predicated on obviousness, would be reversed for the same reasons.").

7. Whether, because claims 12, 17, and 23 of the '528 patent would not have been obvious in view of the entire disclosure of the '416 patent, as a matter of law, those '528 claims would not have been obvious in view of claims 13 or 30 of the '416 patent. *See, e.g., Sanofi*, 492 F. Supp. 2d at 393 ("Because Apotex has failed to prove at trial that the '265 patent was obvious

in light of the '596 patent as a whole, it has also necessarily failed to prove that the '265 patent was obvious in light of the specific claims of the '596 patent.”); *Eli Lilly*, 364 F. Supp. 2d at 910 (“Because under 35 U.S.C. § 103 the narrower selection invention claimed in the '382 patent would not have been obvious from the entire text of the '574 patent, that invention similarly would not have been obvious from the claims of the '574 patent as a matter of law.”), *aff'd*, 471 F.3d 1369 (Fed. Cir. 2006); *Jezl*, 396 F.2d at 1013; *Ornitz*, 376 F.2d at 334; *Land*, 368 F.2d at 884.

8. Whether, because Defendants have infringed claims 12, 17, and 23 of the '528 patent, there can be no finding of lack of utility as a matter of law. *See, e.g., Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 959 (Fed. Cir. 1983) (“A correct finding of infringement of otherwise valid claims mandates as a matter of law a finding of utility under § 101.”).

9. Whether Defendants can prove by clear and convincing evidence that claims 12, 17, and 23 of the '528 patent are invalid for lack of utility under 35 U.S.C. §§ 101 and/or 112, notwithstanding the PTO's conclusion that the '528 patent does in fact meet those requirements. *See, e.g., Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564 (Fed. Cir. 1996) (“In the pharmaceutical arts, our court has long held that practical utility may be shown by adequate evidence of any pharmacological activity.”); *Cross v. Iizuka*, 753 F.2d 1040, 1050 (Fed. Cir. 1985) (“Our predecessor court has noted that adequate proof of any pharmacological activity constitutes a showing of practical utility.”); *Nelson v. Bowler*, 626 F.2d 853, 856 (C.C.P.A. 1980) (“Since it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many compounds as possible, we conclude that adequate proof of any such activity constitutes a showing of practical utility.”); *In re Jolles*, 628 F.2d 1322 (C.C.P.A. 1980).

ENFORCEABILITY

10. Whether Defendants can prove by clear and convincing evidence that the '528 patent is unenforceable on the ground of inequitable conduct. Defendants have the burden to independently establish each element of inequitable conduct. *AstraZeneca Pharms. LP v. Teva Pharms. USA, Inc.*, 2009 U.S. App. LEXIS 21165 (Fed. Cir. 2009).

11. Whether Defendants can prove by clear and convincing evidence that each item of information upon which they rely to support their inequitable conduct defense was material to the patentability of the subject matter claimed in the '528 patent and not merely cumulative or less material than other information already before the PTO. *See, e.g., AstraZeneca*, 2009 U.S. App. LEXIS 21165, at *11-12; *Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, 537 F.3d 1357 (Fed. Cir. 2008).

12. Whether Defendants can prove by clear and convincing evidence that, during the prosecution of the application for the '528 patent or during the reexamination of the '528 patent, each person that Defendants allege committed inequitable conduct (1) owed a duty of candor to the PTO, (2) withheld material information from the PTO or knowingly made a false statement to the PTO, and (3) acted with intent to deceive the PTO. *See, e.g., AstraZeneca*, 2009 U.S. App. LEXIS 21165, at *20-21; *Star Scientific*, 537 F.3d at 1357; *Exergen Corp. v. Wal-Mart Stores, Inc.*, 575 F.3d 1312 (Fed. Cir. 2009).

13. Whether the Court should conclude, after weighing any clear and convincing evidence of materiality and any clear and convincing evidence of intent to deceive, that the "conduct before the PTO was egregious enough to warrant holding the entire patent unenforceable." *Star Scientific*, 537 F.3d at 1365; *see also AstraZeneca*, 2009 U.S. App. LEXIS 21165, at *21-22.

REMEDIES

14. Whether Otsuka is entitled to an order that the effective date of any approval of Defendants' respective ANDAs be a date which is not earlier than the expiration date of the '528 patent. 35 U.S.C. § 271(e)(4)(A). *See also Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 2007 U.S. Dist. LEXIS 19494, at *3-6 (D.N.J. 2007), *aff'd*, 520 F.3d 1358 (Fed. Cir. 2008).

15. Whether Otsuka is entitled to a permanent injunction against Defendants and their officers, agents, attorneys, and employees and those acting in privity or concert with them, enjoining them from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of Defendants' generic aripiprazole products described in Defendants' respective ANDAs during the remaining term of the '528 patent. 35 U.S.C. § 271(e)(4)(B). *See also eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388, 390 (2006).

12. DEFENDANTS' LEGAL ISSUES

Should the Court determine that any issue identified below as an issue of law is more properly considered an issue of fact, it should be so considered.

1. Whether claims 12, 17, and 23 of the '528 patent are invalid for obviousness (35 U.S.C. § 103).

2. Whether claims 12, 17, and 23 of the '528 patent are invalid for obviousness-type double patenting.

3. Whether claims 12, 17 and 23 are invalid under 35 USC sections 101 and/or 112 because the disclosure in the specification of the '528 patent is not adequate to support the use of aripiprazole as an antischizophrenic.

4. Whether the '528 patent is unenforceable for inequitable conduct.

5. Whether Otsuka is entitled to any of its requested remedies.

13. CHOICE OF LAW (If there is any issue as to what state's law is applicable to any count of the complaint, set forth the choice of law question. This issue shall be separately briefed in accordance with an order to be entered herewith).

The parties respectfully submit that there are no choice of law questions.

14. MISCELLANEOUS (Set forth any other matters which require action by, or should be brought to the attention of the Court).

A. Order of Trial

Otsuka's position

Otsuka disagrees with Defendants' statement concerning the order of proof at trial. Otsuka, as Plaintiff and patent holder, should proceed first at trial by presenting a short factual background concerning schizophrenia and the subject matter of Otsuka's patent-in-suit, in particular, aripiprazole. This background will provide the Court with a necessary context for the arguments that follow and is an approach previously ordered by this Court in at least two cases. *See Pfizer Inc. v. Ivax Pharmaceuticals, Inc.*, 2009 WL 2905454, Civil Action No. 07-CV-00174 (DMC) (D.N.J. Sept. 9, 2009); *Novartis Pharmaceuticals Corp. v. Teva Pharmaceuticals USA, Inc.*, 2009 WL 3334850, Civil Action No. 05-CV-1887 (DMC) (D.N.J. October 14, 2009).

Otsuka agrees that following this brief factual presentation, Defendants should proceed with their case in chief followed by Otsuka's rebuttal.

Defendants' position

Defendants have stipulated that the aripiprazole tablets disclosed in their respective ANDAs, if commercially made, used, offered for sale or sold within the United States, or commercially imported into the United States, would fall within the scope of the asserted claims (claims 12, 17 and 23) should those claims be found valid and enforceable. As a result, the only issues to be tried are the invalidity and unenforceability of the '528 patent – issues on which

Defendants bear the burden of proof. Defendants therefore request that they should be permitted to proceed first in the presentation of evidence at the bench trial. Defendants allege that this would result in a more streamlined and efficient trial.

15. JURY TRIALS - Not applicable.

16. NON-JURY TRIALS - Not later than August 2, 2010

A. Each side shall submit to the Judge and opposing counsel a trial brief or memorandum in accordance with Local Civil Rule 7.2B with citation to authorities and arguments in support of its position on all disputed issues of law. In the event a brief shall not be filed, the delinquent party's complaint or defense may be stricken.

The trial briefs shall not exceed 50 pages in length and shall be exchanged simultaneously. Defendants will submit a Joint Trial Brief.

Unless otherwise instructed by the Court, trial briefs are to be filed by August 2, 2010.

B. Each side shall submit to the Judge and other counsel proposed written findings of fact and conclusions of law. There is reserved to counsel the right to submit additional proposed findings of fact and conclusions of law during the course of the trial on those matters that cannot reasonably be anticipated.

Proposed written findings of fact and conclusions of law shall be submitted post trial at a date to be determined by the Court.

17. TRIAL COUNSEL (List the names of trial counsel for all parties).

The following attorneys will try the case for Otsuka: John F. Brenner of Pepper Hamilton, LLP, James B. Monroe, Michael J. Flibbert, Paul W. Browning, Denise Main, Justin J. Hasford, Lawrence L. Ilag and Jeffrey A. Freeman of Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, and Robert L. Baechtold and John D. Murnane of Fitzpatrick, Cella, Harper & Scinto.

The following counsel will appear as trial counsel for Apotex:

James P. White
Daniel R. Cherry

Hartwell P. Morse, III

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The following counsel will appear as trial counsel for Teva and Barr:

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Elizabeth Holland

Maria Luisa Palmese

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18. BIFURCATION (Where appropriate, the issues relating to liability shall be severed and tried to verdict. Thereafter, all issues relating to damages will be tried).

1. Otsuka is not seeking damages for the claims currently set for trial in this matter.

Accordingly, there are no damages issues subject to possible bifurcation at this time. Otsuka, however, reserves the right to seek damages should Defendants engage in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of Defendants' generic aripiprazole products described in Defendants' respective ANDAs before the expiration of the '528 patent. Otsuka further reserves the right to seek its costs and

attorney fees associated with its exceptional case claim pursuant to 35 U.S.C. §§ 285 and 271(e)(4).

2. **Otsuka's additional statement regarding bifurcation:** At Defendants' request, the Court has bifurcated Otsuka's exceptional case claim pursuant to 35 U.S.C. §§ 285 and 271(e)(4). Discovery relating to that claim shall proceed following the Court's entry of judgment on liability. **Defendants's statement regarding bifurcation:** Defendants disagree that they requested bifurcation and that the court has bifurcated Plaintiff's exceptional case claims. Defendants note that they also have an exceptional case claim against Plaintiff pursuant to 35 U.S.C. Section 285. It is within the Court's discretion to decide whether this is an exceptional case and whether the prevailing party is entitled to additional discovery in the event an exceptional case finding is made.

19. ESTIMATED LENGTH OF TRIAL

Otsuka's statement regarding trial length: Defendants have stipulated to infringement of the asserted claims 12, 17 and 23 of the '528 patent and therefore Otsuka need not prove infringement at trial. Moreover, as the '528 patent is presumed valid, Otsuka has no burden of proof regarding Defendants' affirmative defenses and counterclaims that the asserted claims of the '528 patent are invalid or unenforceable. Defendants alone must prove these affirmative defenses and counterclaims by clear and convincing evidence. Accordingly, Otsuka's estimated trial length will depend on what arguments Defendants intend to pursue at trial. Otsuka objects to Defendants' estimated trial length of 10 days. Defendants' hodge-podge of invalidity and unenforceability allegations as set forth in the contested facts section of this Pretrial Order are numerous. Moreover, at this time, based on Defendants' identification of 47 fact and expert witnesses that Defendants seek to have testify live or by deposition and Defendants' listing of nearly 1000 trial exhibits, Otsuka estimates the parties require at least 20 days to try this case.

Defendants' statement regarding trial length: Defendants estimate, based on the number of witnesses and the defenses asserted, that 10 days should be sufficient for trial.

 20 days (Otsuka's estimate) or 10 days (Defendants' estimate) **DAYS FOR LIABILITY**

and

 0 **DAYS FOR DAMAGES.**

AMENDMENTS TO THIS PRETRIAL ORDER WILL NOT BE PERMITTED UNLESS THE COURT DETERMINES THAT MANIFEST INJUSTICE WOULD RESULT IF THE AMENDMENT IS DISALLOWED.

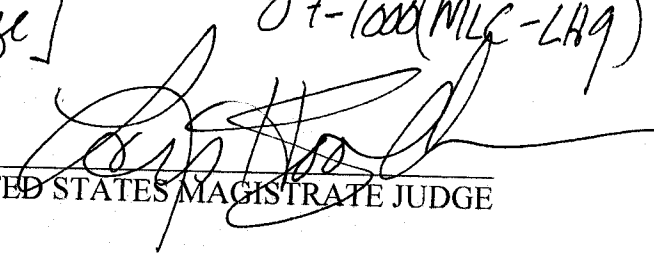
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07-1000(MLC-LHG)


UNITED STATES MAGISTRATE JUDGE

DATED: July 14, 2010
(EXHIBIT LIST TO FOLLOW)